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Phenylethane derivatives and acid addition salts thereof for enhancing the growth rate of meat-producing animals, improving the efficiency of feed utilization thereby and/or improving the lean meat to fat ratio thereof.

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There is provided a method for enhancing the growth rate of meat-producing animals, improving the efficiency of feed utilization thereby, and/or improving the lean meat to fat ratio thereof, which involves, orally or parenterally, administering to said animals a growth-enhancing amount of a phenylethane compound or the acid addition salt thereof.

EP 0 049 728 A2

PHENYLETHANE DERIVATIVES AND ACID ADDITION
SALT THEREOF FOR ENHANCING THE GROWTH RATE OF
MEAT-PRODUCING ANIMALS, IMPROVING THE
EFFICIENCY OF FEED UTILIZATION THEREBY AND/OR
IMPROVING THE LEAN MEAT TO FAT RATIO THEREOF

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SUMMARY OF THE INVENTION

Substitution products of 1-(amino-dihalophenyl)
-2-aminoethanes, and the acid addition salts thereof,
are disclosed in United States Patent 3,536,712, issued
October 27, 1970. Specifically, methods for the synthesis
10 of said compounds are disclosed as useful for enhancing
the blood circulation, and as bronchodilators, analgesics,
sedatives, antipyretics, antiphlogistics and antitussives
in warm-blooded animals. However, only the analgesic
utility is exemplified. The preparation of other related
15 1-(amino-dihalophenyl)-2-aminoethanols and their deriva-
tives are disclosed in Japanese Kokai 77 83,619 (Chemical
Abstracts, 87,201061r), German Offenlegungsschrift
2,804,625 (1979), German Offenlegungsschrift 2,157,040
(1973), German Offenlegungsschrift 2,261,914 (1974),
20 European Patent Application 8,715 (1980), Netherlands
Patent Application 7,303,612 (1973). These applications

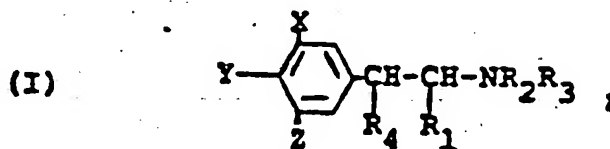
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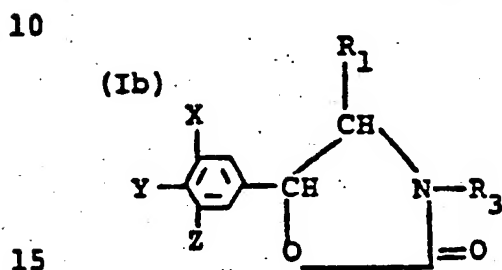
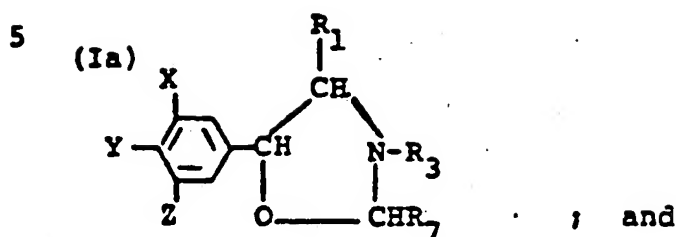
disclose uses selected from analgesics, broncholytic,
5 antiinflammatory, uterine spasmolytic, β -blocking activities, *
antispasmodic activity on cross-striated muscle structure,
for tocology, reducing blood pressure by peripheral
vasodilation and mobilizing body fat, and for treating
allergies. There is no indication or suggestion in any
10 of these disclosures that said compounds are effective
as growth-promoting agents for meat-producing animals,
such as poultry, cattle, sheep or the like; nor is
there any suggestion that said compounds improve the
efficiency of feed utilization by said meat-producing
15 animals.

In accordance with the process of the invention,
it has been found that the growth rate of meat-producing
animals such as chickens, turkeys, rabbits, sheep, swine,
goats and cattle, including calves, can be increased,
20 the efficiency of feed utilization thereby measurably improved,
and the lean meat to fat ratio improved by the oral or parenteral
administration to said animals of an effective amount of a compound
selected from the group consisting of:



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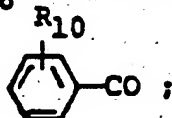
wherein, X is hydrogen, halogen or -CN;

Y is hydrogen, NR_8R_9 or NHCOR_5 ;

20 Z is hydrogen, halogen, OH, CN, CF_3 , COOR_1 , CONH_2 , $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ alkoxy, NO_2 , $\text{C}_1\text{-C}_4$ -dialkylaminomethyl or hydroxymethyl;

R_1 is hydrogen or $\text{C}_1\text{-C}_4$ alkyl;

25 R_2 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_5$ alkanoyl or

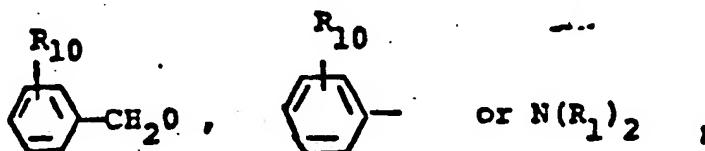


R_3 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, methoxypropyl, $\text{C}_3\text{-C}_4$ alkenyl, phenyl, 2-hydroxyethyl, α,α -

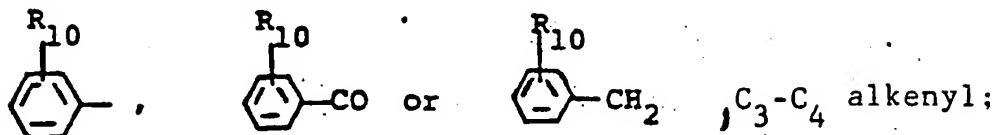
30 dimethylphenethyl, benzyl, 3-phenylpropyl or 3-(4-carbomethoxyphenyl)propyl; and when R_2 and R_3 are taken together with the nitrogen to which they are attached, they represent morpholino or $\text{N}'\text{-C}_1\text{-C}_4$ alkylpiperazino;

R_4 is hydrogen, OH, OR_6 or SR_{11} ;

35 R_5 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ alkoxy,



5 R_6 is C_1-C_6 alkyl, C_2-C_5 alkanoyl,



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R_7 is hydrogen, C_1-C_4 alkyl or phenyl;

R_8 is hydrogen, C_1-C_4 alkyl or C_3-C_4 alkenyl;

R_9 is hydrogen, C_1-C_6 alkyl, C_4-C_6 cycloalkyl, C_3-C_4 alkenyl, or benzyl; and when R_8 and R_9 are taken together

15 with the nitrogen to which they are attached, they

represent pyrrolidino; R_{10} is chloro, dichloro, methyl,

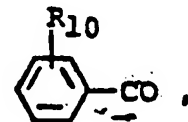
dimethyl, methoxy, dimethoxy or nitro; R_{11} is C_1-C_6 alkyl, phenyl or benzyl; with the provisos that when

R_3 is phenyl, 2-hydroxyethyl, α,α -dimethylphenethyl,

20 C_3-C_6 cycloalkyl, benzyl, methoxypropyl, 3-phenylpropyl, or 3-(4-carbomethoxyphenyl)propyl, R_2 is hydrogen;

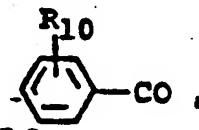
and when R_3 is hydroxyethyl, R_4 is hydroxyl and the compound is (I); and when R_6 is alkanoyl or

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R_2 and R_3 are substituents other than hydrogen, except when R_3 is an alkyl or substituted alkyl group which contains a tertiary carbon attached to nitrogen; and

30 when Y is hydrogen, X and Z are halogen, and R_2 is hydrogen, C_3-C_5 alkanoyl or



35 R_3 is isopropyl, 2-butyl, or t-butyl; and when R_8 is C_1-C_4 alkyl or C_3-C_4 alkenyl, R_9 is hydrogen,

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- 5 C₁-C₄ alkyl or C₃-C₄ alkenyl; and when Z is OH, X and Y are hydrogen; and that at least one of X, Y, and Z represents a substituent other than hydrogen; and when X is -CN, Z is -CN; and when Z is hydroxymethyl, R₄ is OH; and when Z is a group other than halogen, Y is NR₈R₉ or NHCOR₅; and when R₅ is N(R₁)₂, R₄ is OH; and further provided that when X is hydrogen or halogen, and Y is hydrogen, NH₂ or NHCOR₅, and Z is hydrogen, halogen or OH, then R₄ cannot be hydrogen, OH or OR₆ where R₆ is C₁-C₆ alkyl; racemic mixtures of the above - identified compounds and the optically active isomers, and non-toxic, pharmacologically acceptable acid addition salts thereof.

A preferred group of compounds for use in the method of this invention have the above formula I structure wherein X is hydrogen or halogen; Y is hydrogen, NR₈R₉ or NHCOR₅; Z is halogen, OH, CN, CF₃, COOR₁, CONH₂, methyl, methoxy, NO₂, C₁-C₄ dialkylaminomethyl, or hydroxymethyl; and the remaining groups are as hereinbefore defined; or a non-toxic, pharmacologically acceptable acid addition salt thereof.

Another preferred group of compounds for use in the method of this invention have the above formula I structure wherein X is hydrogen, chlorine, or bromine; Y is hydrogen or NR₈R₉; Z is chlorine, bromine, CN, CF₃; R₁ is hydrogen or methyl; R₄ is OH, OR₆, SR₁₁; R₆ is C₁-C₆ alkyl, benzyl, C₂-C₅ alkanoyl, or benzoyl; or a non-toxic, pharmacologically acceptable acid addition salt thereof.

The most preferred compounds for use in this invention are: 4-amino-N-tert-butyl-3,5-dichloro-8-methoxyphenethylamine; N-tert-butyl-

- 5 3,5-dichloro-8-methoxy-4-methylaminophenethylamine; α -[(tert-butylamino)methyl]-3,5-dichloro-4-isopropylaminobenzyl alcohol
 5-[2-(tert-butylamino)-1-hydroxyethyl]-3-chloroanthranilonitrile;
 5-[2-(tert-butylamino)-1-hydroxyethyl]anthranilonitrile; methyl
 -5-[2-(tert-butylamino)-1-hydroxyethyl]-3-chloroanthronilate;
 10 4^1 -[2-(tert-butylamino)-1-hydroxyethyl]-2 1 ,6 1 -dichlorovaleranilide;
 benzyl-4-[2-(tert-butylamino)-1-hydroxyethyl]-2,6-dichlorocarbon-
 ilate; 5-acetylanthranilonitrile; 4-amino-N-tert-butyl-3,5-dichloro-
 -8-(methylthio)phenethylamine; N-tert-butyl-3,5-dichloro-8-methoxy-
 phenethylamine; α -[(tert-butylamino)-methyl]-3,5-dichloro-4-methy-
 15 laminobenzyl alcohol; α -[(tert-butylamino)methyl-3,5-dichloro-4-
 dimethylaminobenzyl alcohol; 4-amino-3,5-dichloro- α -{[(3-phenyl-
 propyl)amino]methyl}benzyl alcohol; 4-amino-3,5-dichloro- α -{[2,2-
 dimethylphenethyl)amino]methyl}benzyl alcohol; 4-amino-N-tert-
 butyl-3,5-dichloro-8-ethoxyphenethylamine; methyl-p-[3-[(4-
 20 amino-3,5-dichloro-8-hydroxyphenethyl)amino]propyl]benzoate;
 methyl-4-[2-(tert-butylamino)-1-hydroxyethyl]-2,6-dichlorocartanilate;
 4^1 -[2-(tert-butylamino)-1-hydroxyethyl]-2 1 ,6 1 -dichloroacetanilide;
 5-[2(tert-butylamino)-1-hydroxyethyl]-3-chloroanthranilonitrile; 4-
 amino-8-(benzyloxy)-N-tert-butyl-3,5-dichlorophenethylamine and the
 25 non-toxic, pharmaceutically acceptable acid addition salts thereof.

Although it is evident from the above discussion
 that certain compounds represented by formula I above
 are described in the literature, many compounds represented
 by formula I are new and unobvious. The novel and
 30 unobvious compounds of the present invention are represented
 by the structure of formula I,

5 wherein X is hydrogen, halogen or -CN;

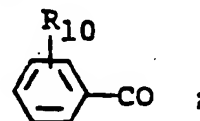
Y is hydrogen, NR_8R_9 or NHCOR_5 ;

Z is halogen, -CN, CF_3 , COOR_1 , CONH_2 , $\text{C}_1\text{-C}_4$ alkyl,

$\text{C}_1\text{-C}_4$ alkoxy, NO_2 or $\text{C}_1\text{-C}_4$ dialkylaminomethyl;

R_1 is hydrogen or $\text{C}_1\text{-C}_4$ alkyl;

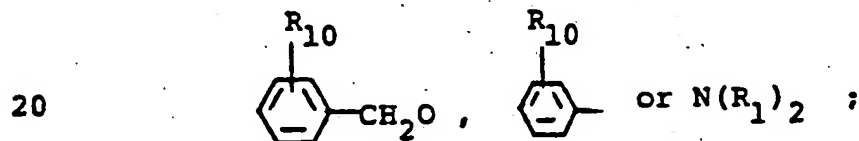
10 R_2 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_5$ alkanoyl or



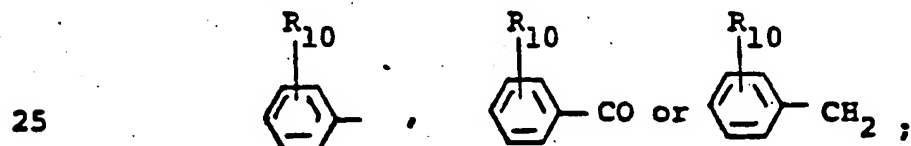
R_3 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_4$ alkenyl, phenyl or benzyl;

R_4 is OH, OR_6 or SR_{11} ;

R_5 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ alkoxy,



R_6 is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_5$ alkanoyl,



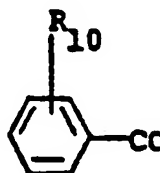
R_8 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl or $\text{C}_3\text{-C}_4$ alkenyl;

R_9 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_4\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_4$ alkenyl, or benzyl; R_{10} is hydrogen, chloro, dichloro, methyl, dimethyl, methoxy, dimethoxy or nitro;

30 R_{11} is $\text{C}_1\text{-C}_6$ alkyl, phenyl, benzyl; with the provisos that when Y is NH_2 , NECH_3 , NEC_2H_5 or NHCOR_5 ,

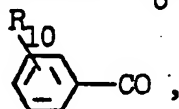
R_4 is OR_6 or SR_{11} ; and when Y is hydrogen, X and Y are halogen, R_2 is hydrogen, $\text{C}_2\text{-C}_5$ alkanoyl or

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and R_3 is isopropyl, 2-butyl or t-butyl; and when X is -CN, Z is -CN; and when R_6 is alkanoyl or



5

R_2 and R_3 are substituents other than hydrogen, except when R_3 is an alkyl or a substituted alkyl group which contains a tertiary carbon attached to nitrogen; and when R_8 is C_1-C_4 alkyl, or C_3-C_4 alkenyl, R_9 is hydrogen, C_1-C_4 alkyl or C_3-C_4 alkenyl; and further provided that when X and Z are halogen and Y is hydrogen or NH_2 , then R_4 cannot be hydrogen, OH or OR_6 where R_6 is C_1-C_6 alkyl. Racemic mixtures of the above identified compounds and the optically active isomers, and non-toxic pharmacologically acceptable acid addition salts thereof.

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A preferred group of the novel compounds of this invention have the above structure wherein X = hydrogen or halogen; Y is hydrogen, NR_8R_9 , or $NH-COR_5$; Z is halogen, CN, CF_3 , COOR, $CONH_2$, methyl, methoxy, NO_2 , C_1-C_4 dialkylaminomethyl; R_1 is hydrogen, or methyl, R_2 is hydrogen, C_1-C_4 alkyl, C_3-C_4 alkenyl, C_2-C_4 alkanoyl or benzoyl; R_3 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 alkenyl, benzyl; with the above provisos, and further provided that when X and Z are halogen and Y is hydrogen or NH_2 , then R_4 cannot be hydrogen, OH or OR_6 when R_6 is C_1-C_6 alkyl.

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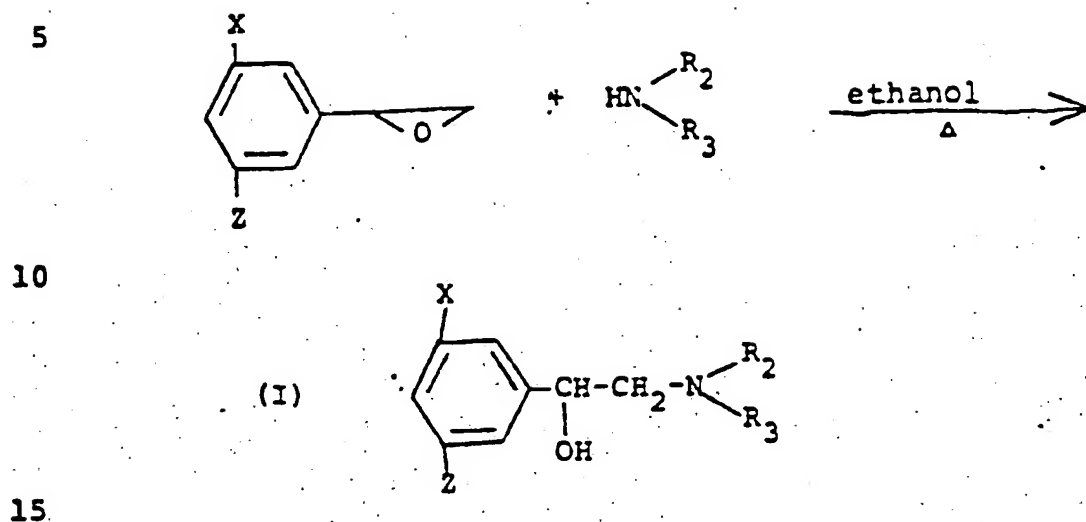
A most preferred group of novel compounds of this invention have the above structure wherein X = hydrogen, chlorine, bromine; Z is chlorine, bromine, CN, CF_3 , COOH, $COOCH_3$, $COOC_2H_5$, $CONH_2$; R_1 is hydrogen; R_2 is hydrogen, C_1-C_4 alkyl; R_3 is hydrogen, C_1-C_4 alkyl; with the above provisos, and further provided that when X and Z are halogen and Y is hydrogen or NH_2 , then R_4 cannot be hydrogen, OH or OR_6 where R_6 is C_1-C_6 alkyl.

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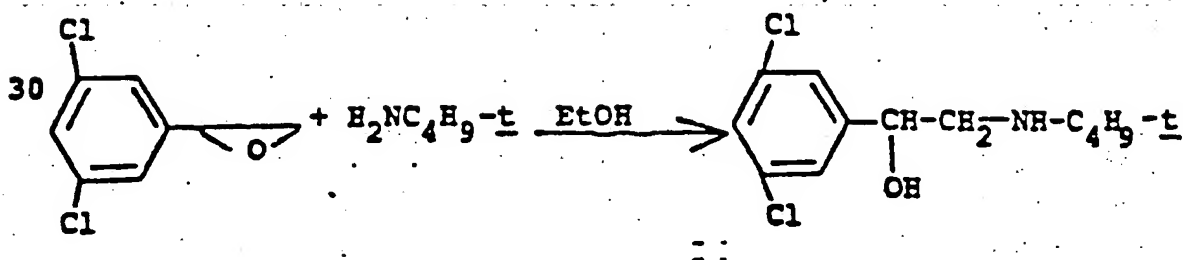
It is found, that formula (I) compounds below (wherein Y is hydrogen) can be prepared by the condensation of an appropriately substituted styrene oxide with the appropriately substituted amine in the presence of an inert solvent, such as a lower alcohol at or near the boiling point of same, as shown below:

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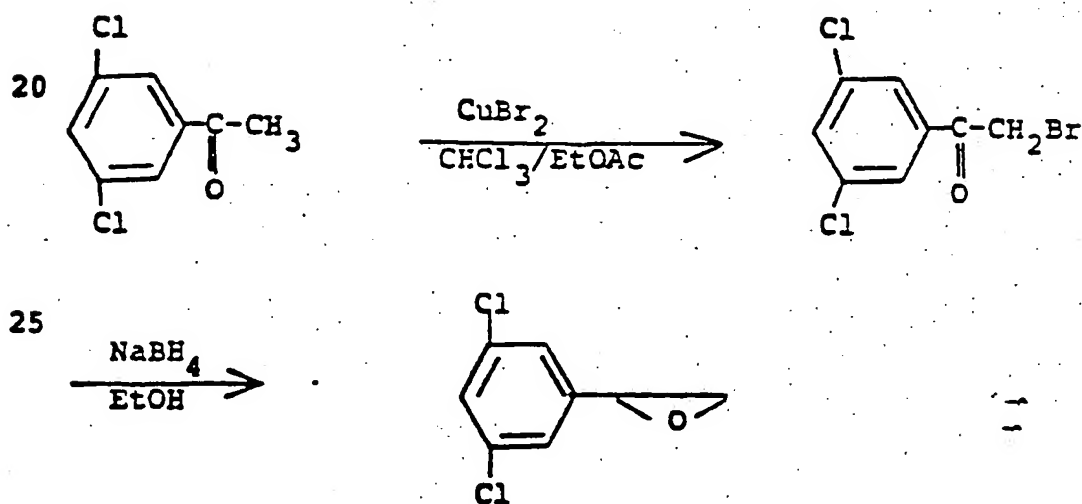
20 wherein X and Z are halogen, R₂ and R₃ are as hereinabove defined and Y is hydrogen. Thus, 3,5-dichlorostyrene oxide can be reacted with an equimolar or molar excess of t-butylamine in ethanol at reflux from about one to about eight hours, or until the reaction is essentially complete and the desired α -[(t-butylamino)methyl]-3,5-

25 dichlorobenzyl alcohol is obtained as illustrated below:



5 The thus obtained product can be purified by known procedures, such as chromatography or recrystallization of salts thereof.

The above styrene oxide is made by reducing the corresponding phenacyl bromide with NaBH_4 at or
 10 below 5°C in the presence of an anhydrous lower alcohol, such as ethanol. The phenacyl bromide intermediate is prepared by brominating the appropriately substituted acetophenone with CuBr_2 in the presence of chloroform and ethyl acetate. The above sequence may be graphically
 15 illustrated as follows:

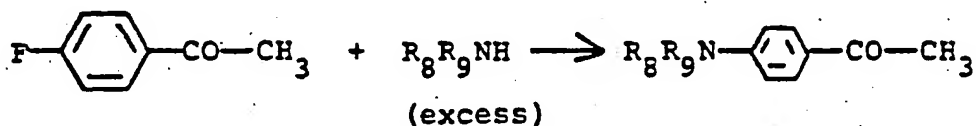


Alternatively, a formula (I) compound wherein Y is hydrogen may be prepared from the corresponding formula (I) compound wherein Y is amino, via a deamination
 35 reaction, by dissolving the amine in 50-52% aqueous

5 hypophosphorous acid (H_3PO_2). The solution is chilled below 10°C , and an equimolar or excess amount of sodium nitrite is added to an aqueous solution with stirring over a period of time. On completion of the addition, the reaction mixture is warmed to room temperature
10 and stirred for an additional period of time. The product is then recovered from the reaction mixture by standard laboratory procedures and purified if so desired.

The preparation of 4-substituted aminoacetophenones required for the preparation of 4-substituted
15 phenylethane derivatives which are now found to be useful for raising meat-producing animals, is exemplified as follows:

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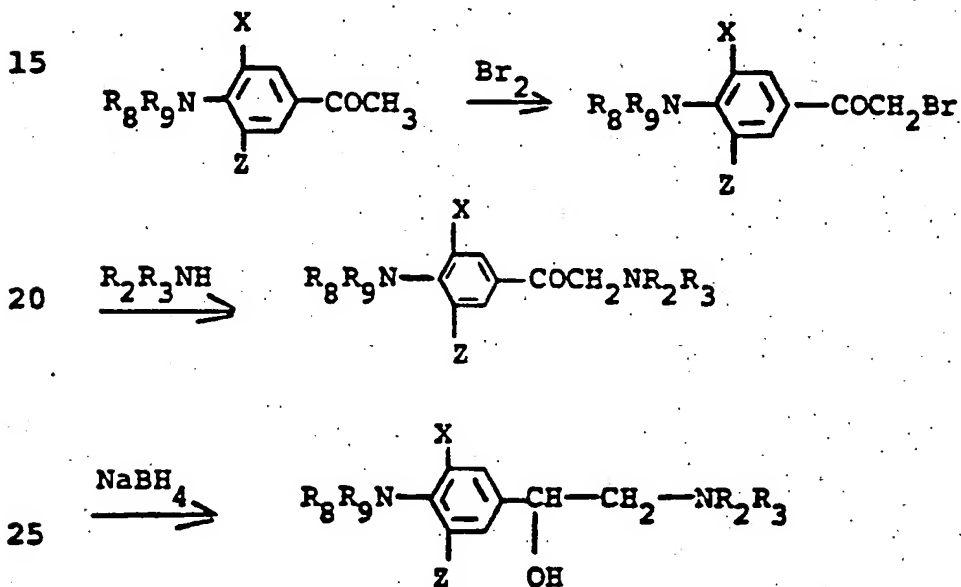


25 The fluorine displacement is carried out with excess amine in the presence or absence of a solvent; and, if a solvent is required, water appears to be the most useful. With volatile amines, the reaction is conducted in a sealed vessel and generally temperatures of $50 - 100^\circ\text{C}$ are sufficient to complete the reaction.

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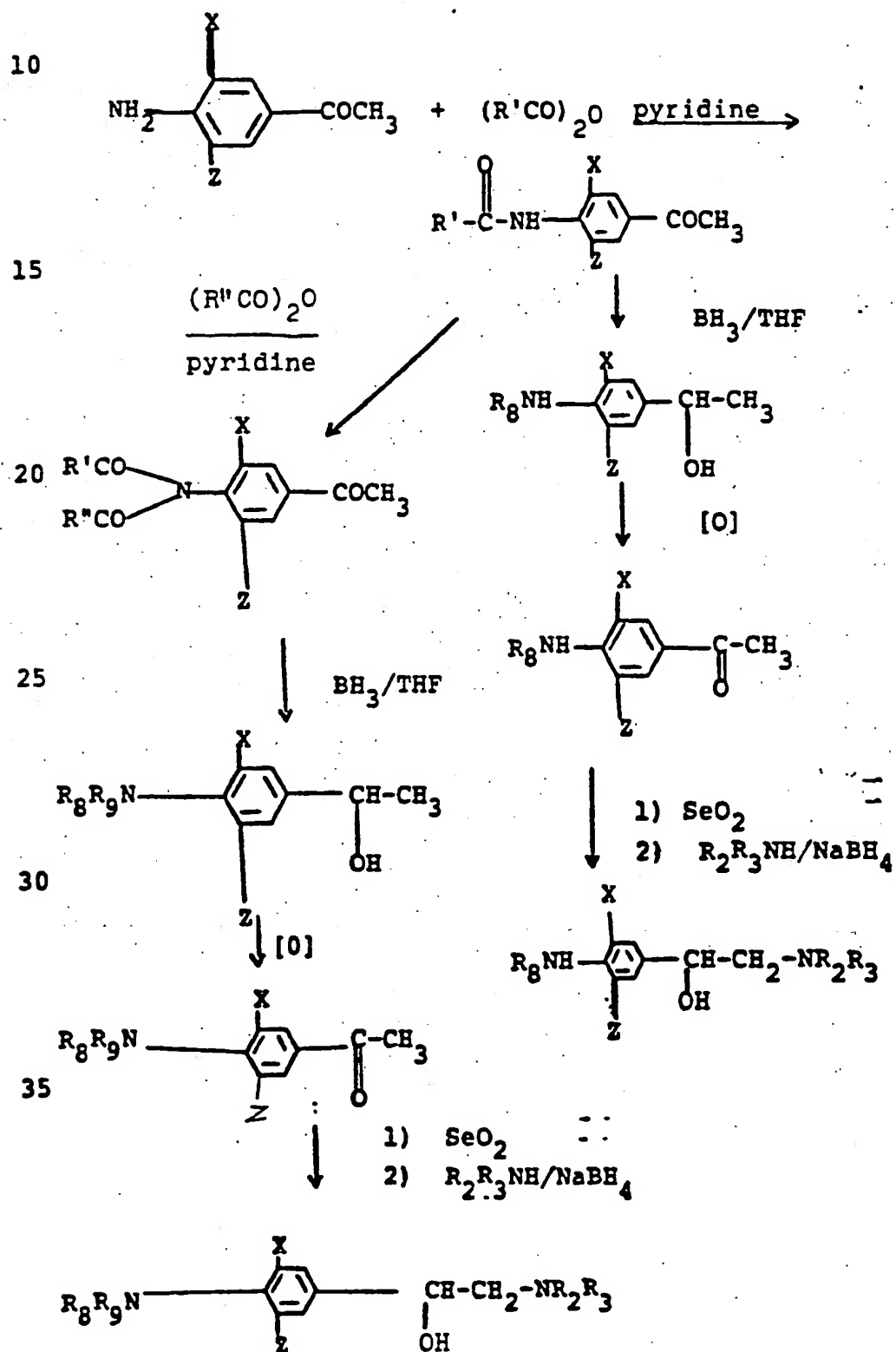
Chlorination and bromination of these aminoacetophenones may be conducted with N-chlorosuccinimide and N-bromosuccinimide in toluene, chlorobenzene or dichlorobenzene at $90 - 100^\circ\text{C}$. Iodination may be
35 conducted with $\text{NaI}/\text{N,N}$ -dichlorobenzenesulfonamide or iodine monochloride in acetic acid.

5 By reacting these acetophenones with bromine
 in chloroform or methylene chloride, the corresponding
 phenacyl bromides are prepared. These phenacyl bromides
 are then reacted with R_2R_3N amines and the aminoketones
 are reduced with $NaBH_4$ or $NaCNBH_3$ by conventional
 10 techniques described in references cited hereinbefore.
 Naturally, compounds which contain groups reactive
 to halogen, such as when R_8 is alkenyl, require other
 approaches that are discussed below.



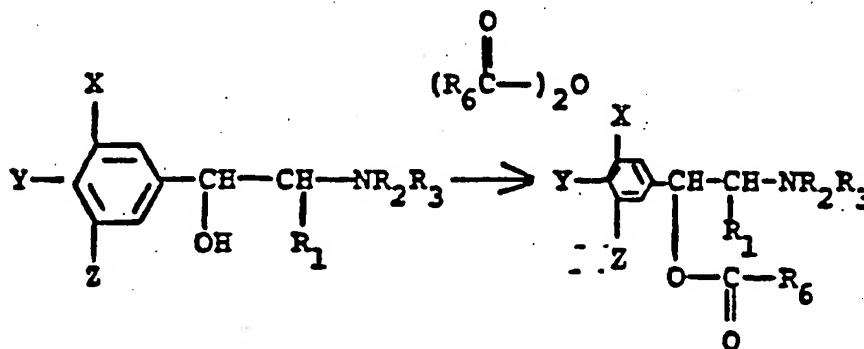
wherein X and Z are hydrogen, chlorine, or bromine
 35 and R_2 and R_3 are hydrogen, C_1-C_4 alkyl, or C_2-C_3
 alkenyl groups.

5 The compounds of formula I, wherein R_8 and R_9 are groups other than both being hydrogen are also prepared by the following general scheme:



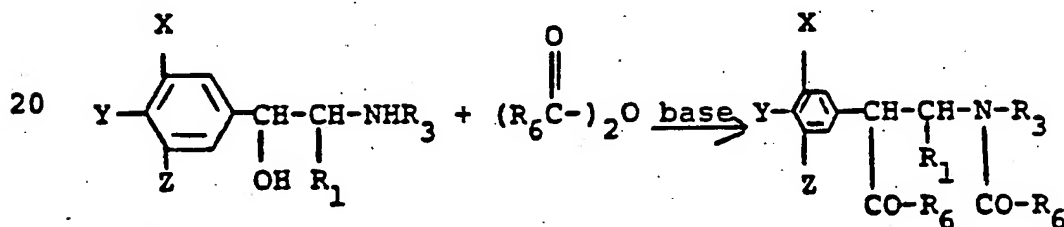
5 The methods utilized in the above scheme
 are either reported in references cited hereinbefore
 or by conventional methods. Oxidation of the alcohol
 may be conducted with chromic acid (Jones Reagent),
 10 MnO_2 , pyridinium chlorochromate, or other oxidizing
 agents. Where X or Z are the BH_3 -reducible groups,
 CN, COOR, or CONH_2 , the appropriate acetophenones
 are prepared by displacement of X or Z represented
 by bromine with CuCN/DMF at $100 - 160^\circ\text{C}$ by the conven-
 15 tional method, after reduction of the acylated aminoaceto-
 phenones in the first step followed by re-oxidation
 in the second step of the above procedure. The cyano
 substituted-amino-acetophenones are then converted
 to their corresponding ethanolamines, which are then
 converted to the desired esters, acids, and amides
 20 by conventional methods, such as $\text{R}_1\text{OH/acid} \rightarrow \text{esters}$,
 hydrolyses $\rightarrow \text{acids}$ and partial hydrolyses $\rightarrow \text{amides}$.

Furthermore, compounds of the following
 structure are prepared by allowing the corresponding
 ethanolamines to react with an equivalent or slight
 25 excess of the acid anhydrides with or without organic
 bases such as tertiary amines or pyridine. The reactions
 are conducted in inert solvents

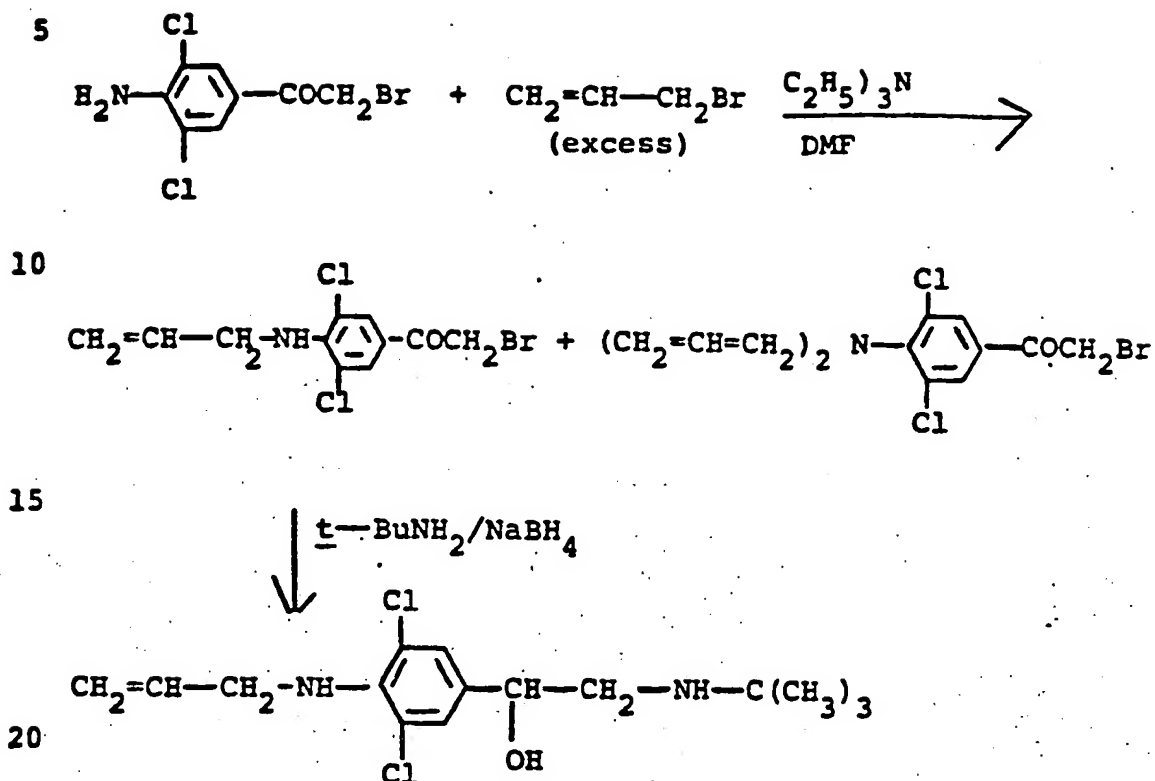


5 such as chlorinated hydrocarbons, or aromatic solvents
 at 0 - 25°C. Reaction of the anhydride at the hydroxyl
 group proceeds well provided R₂ and R₃ are groups
 other than hydrogen and when R₂ is hydrogen, R₃ is
 a substituent containing a tertiary carbon attached
 10 to nitrogen.

Compounds of the following structure which
 contain alkanoyl or aroyl groups on ethanolamine moiety
 are readily prepared by using two equivalents or more
 of the acid anhydrides in the presence of a tertiary
 15 amine, such as triethylamine, or pyridine in an inert
 solvent (CH₂Cl₂, CHCl₃, toluene, etc.) at 50 - 100°C.



25 Additionally, Formula I compounds, wherein
 R₈ and R₉ are selected from hydrogen and C₃-C₄ alkenyl,
 are prepared by alkenylation of 4-amino-3,5-disubstituted
 phenacyl bromides in dimethylformamide (DMF) in the
 presence of an acid acceptor, such as triethylamine
 30 or sodium carbonate, at 70 - 100°C to afford mono-
 and dialkenylated products which are separated and
 converted to I by conventional methods. The following
 scheme illustrates above-described general method:



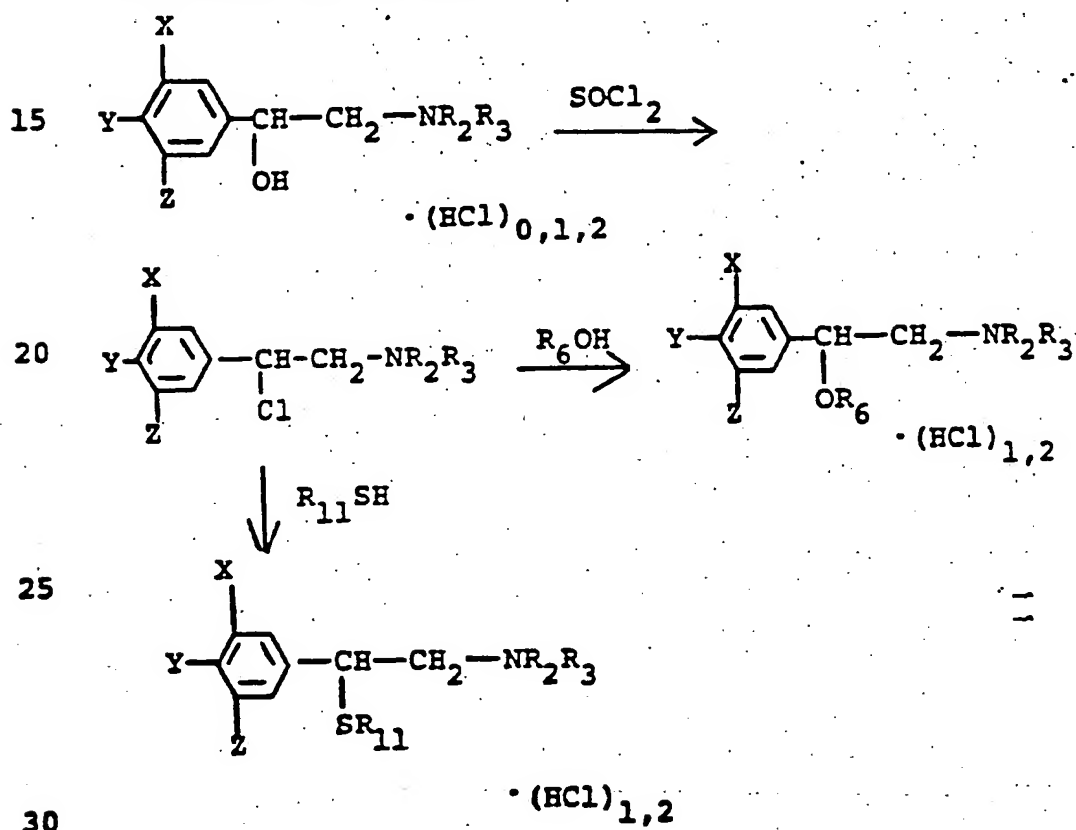
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Formula (I) compounds wherein R_4 is OR_6 and SR_{11} , wherein R_6 and R_{11} are as hereinabove defined, may be prepared by converting the alcohol ($R_4=\text{OH}$) with thionyl chloride under an inert blanket of gas such as nitrogen at a temperature range of from about 0 to 10°C and preferably at 0 to 5°C for a reaction period sufficient to essentially complete the reaction. The thus obtained

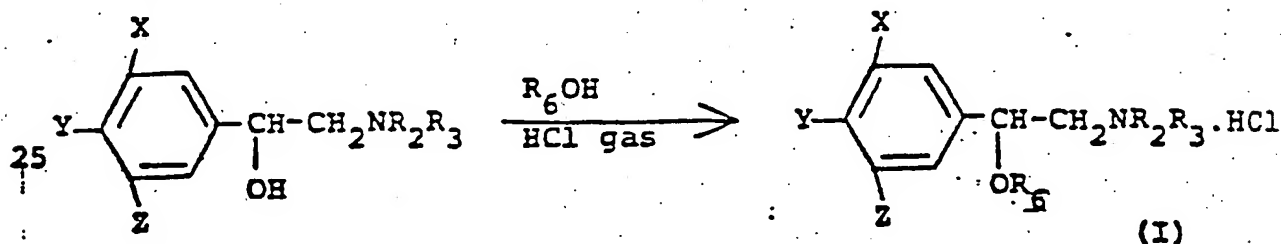
5 halo compound is isolated by conventional methods and is then reacted with the appropriate alcohol or mercaptan, under an inert blanket of gas, such as nitrogen at a temperature range of from about 0 to 50°C. The formula (I) product thus obtained is then isolated
 10 by standard laboratory methods and purified, if so desired. The above reaction sequence may be graphically illustrated as follows:



5 wherein X, Y, Z, R₂, R₃, R₆ and R₁₁ are as hereinabove defined.

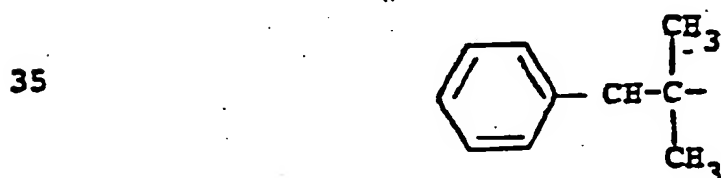
These displacement reactions may also be performed by using an excess of alkoxide (R₆O⁻) or mercaptide (R₁₁S⁻) in an inert solvent such as tetra-
10 hydrofuran to afford the above ethers and thioethers in a similar manner.

Alternatively, a formula (I) compound wherein R₄ is OR₆ may be prepared by dissolving the corresponding formula (I) compound wherein R₄ is OH in the corresponding
15 R₆OH alcohol and saturating the thus obtained solution with dry HCl gas. The reaction mixture is then stirred at room temperature for a period of time sufficient to essentially complete the reaction and the product is then isolated by standard laboratory procedures
20 and purified, if so desired. This reaction sequence may be illustrated as follows:



wherein X, Y, Z, R₂, R₃ and R₆ are as hereinabove
30 defined.

In the present specification and claims, the term α, α-dimethylphenethyl means a structure having the following configuration:



5 Animal feed supplements can be prepared by admix-
ing about 10% to 75% by weight of the phenylethane derivative
of acid addition salt thereof, with about 90% to 25% by
weight of a suitable carrier or diluent. Carriers suit-
able for use to make up the feed supplement compositions
10 include the following: alfalfa meal, soybean meal, cotton-
seed oil meal, linseed oil meal sodium chloride, cornmeal,
can molasses, urea, bone meal, corncob meal and the like.
The carrier promotes a uniform distribution of the active
ingredient in the finished feed into which the supplement
15 is blended. It thus performs an important function by
ensuring proper distribution of the active ingredient
throughout the feed.

 If the supplement is used as a top dressing for
feed, it likewise helps to ensure uniformity of distribution
20 of the active material across the top of the dressed feed.

 For parenteral administration, the phenylethane
derivative may be prepared in the form of a paste or
pellet and administered as an implant, usually under the
skin of the head or ear of the animal in which enhanced
25 growth rate and/or improved efficiency of feed utiliza-
tion is sought.

 In practice, parenteral administration generally
involves injection of a sufficient amount of the above-
said phenylethane derivative to provide the animal with
30 from 0.001 to 50 mg/kg of body weight of the active
ingredient. The preferred dosage level for cattle is
the range of from 0.001 to 25 mg/kg of body weight of
the active phenylethane derivative. The preferred dose
level of said phenylethane derivative for poultry is
35 about 0.001 to 35 mg/kg of animal body weight and the
preferred dose level of said phenylthane derivative for
sheep and goats is 0.001 to 40 mg/kg of animal body weight.
The preferred dose level for rabbits is 0.001 to 35 mg/kg
of animal body weight.

When orally administered in the feed, generally about 0.01 to 300 grams per ton of feed of the above-identified phenylethane derivative or acid addition salt thereof, is effective for enhancing the growth rate and improving the efficiency of feed utilization by the above-mentioned meat-producing animals.

Since the effective and preferred dietary levels of the active ingredient vary somewhat from species to species in the above-mentioned animals, said levels for each animal species are listed in Table I below on a gram per ton of feed basis:

TABLE I

Compound	Effective Feed Level g/Ton	Preferred Level g/Ton	Animal
Formula (I)	0.1-200	1-100	Sheep, Goats
	0.01-50	0.1-10	Chickens, Rabbits
	0.01-50	0.1-10	Turkeys
	0.1-300	1-100	Cattle & Swine

Animal feed compositions which will provide the desired growth promotion and feed efficiency in the above-mentioned animals can be prepared by admixing the phenylethane derivative or acid addition salt thereof, or an animal feed supplement containing said compound, with a sufficient quantity of an appropriate animal feed to provide the desired level of active compound in said feed.

5 Past formulations can be prepared by dispersing
the active phenylethane derivative in a pharmaceutically
acceptable oil such as peanut oil, sesame oil, corn
oil or the like.

10 Pellets containing an effective level of
the phenylethane derivative can be prepared by admixing
the above-said active ingredient with a diluent such
as carbowax, biodegradable polymers, carnauba wax,
or the like. A lubricant, such as magnesium stearate
or calcium stearate may be added to improve the pelleting
15 process if desired.

 It is, of course, recognized that more than
one pellet may be administered to an animal to achieve
the desired dose level which will provide the increased
growth rate and/or improve efficiency of feed utilization
20 by said animal. Moreover, it has been found that
additional implants may also be introduced periodically
during the treatment period in order to maintain the
proper drug release rate in the animal's body.

 In addition to enhanced growth promotion
25 and improved efficiency of feed utilization by meat-
producing animals, the compounds of the present invention
have the added advantage that, at selected levels
of administration, they increase the deposition of
lean meat (i.e., muscle or protein) in said animals
30 and improve the carcass quality thereof by increasing
the ratio of lean meat to fat in the animals receiving
them. This biological response has substantial advantage
to poultrymen, cattlemen, and swine, sheep and goat
producers since administration of said compounds at
35 selected levels yields leaner animals which command
premium prices from the meat industry.

5 These and other advantages of the present invention will become apparent from the examples set forth below. Such examples are provided only by way of exemplification and are not intended to be expressions of limitations on the invention.

10

EXAMPLE 1

Evaluation of Test Compounds as Animal Growth Promoters

CFI female mice from Carworth Farms are received when they are six weeks old. They are housed ten to a cage in air-conditioned rooms (72°F to 76°F) with automatically controlled lights, 14 hours on and 10 hours off. The basal diet used in these studies is Purina Laboratory Chow (see description below), which is supplied ad libitum. Water is allowed ad libitum.

20

Thirteen days after arrival, the mice are weighed in groups of ten and assigned at random to the different treatments. The concentration of the different compounds in the diet is indicated in the following tables. Twelve days later the mice are weighed again, and the experiment terminated. Test data are provided in Table II below wherein data are reported as percentage gain over controls. Different control animals are used for each test. The following is description of the diet to which the growth-promoting compounds were added.

30

DIET

Guaranteed Analysis

	Crude protein not less than	23.0%
	Crude fat not less than	4.5%
35	Crude fiber not more than	6.0%
	Ash not more than	9.0%

5

Ingredients

Meat and bone meal, dried skimmed milk, wheat germ meal, fish meal, animal liver meal, dried beet pulp, ground extruded corn, ground oat groats, soybean meal, dehydrated alfalfa meal, cane molasses, animal fat
10 preserved with BHA, vitamin B₁₂ supplement, calcium pantothenate, choline chloride, folic acid, riboflavin supplement, brewer's dried yeast, thiamin, niacin, vitamin A supplement, D-activated plant sterol, vitamin E
15 iodized salt, ferric ammonium citrate, iron oxide, manganous oxide, cobalt carbonate, copper oxide, zinc oxide.

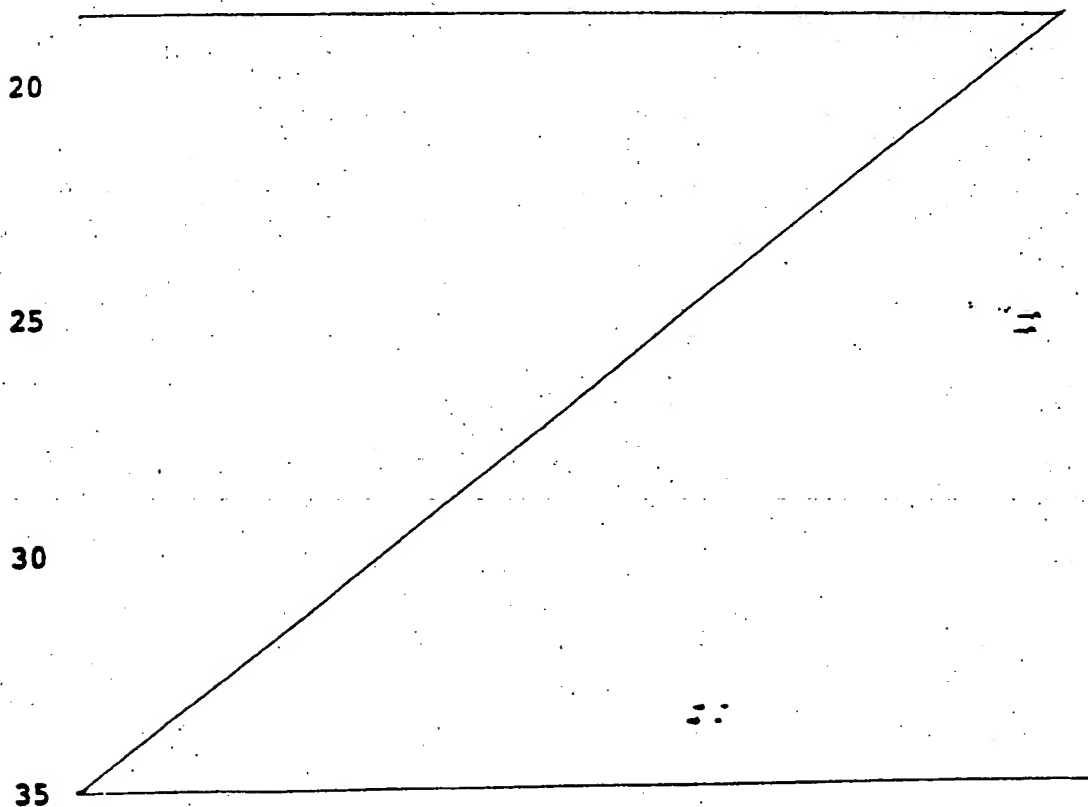


TABLE II
Evaluation of Test Compounds as Animal Growth Promoters

<u>Compound</u>	<u>Dosage</u> <u>(ppm)</u>	<u>Gain</u> <u>(grams)</u>	<u>% Gain Over</u> <u>Controls</u>
4'-[2-(tert-butylamino)-1-hydroxyethyl]-2'-chloro- acetanilide	200	16.8	+107.9
	100	18.4	+127.7
4-Amino- α -[(tert-butylamino)methyl]-3,5-diiodobenzyl alcohol hydrochloride	200	21.1	+27.1
	100	20.0	+20.5
4-Amino-N-tert-butyl-3,5-dichlorophenethylamine hydrochloride	50	12.3	7.9
α -(Aminomethyl)-m-chlorobenzyl alcohol hydrochloride	200	15.8	+4.6
	100	15.8	+4.6
4-Amino- α -[(tert-butylamino)methyl]-3,5-diiodobenzyl alcohol hydrochloride	200	21.1	+27.1
	100	20.0	+20.5

TABLE II (continued)
Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
α -[(Tert-butylamino)methyl]-3,5-dichloro-4-methylaminobenzyl alcohol	200 50	16.0 21.9	0 +36.9
4-Amino-3,5-dichloro- α -[(3-phenylpropyl)aminomethyl]benzyl alcohol	200 50	16.9 18.9	+ 5.6 +18.1
α -[(Tert-butylamino)methyl]-3,5-dichloro-4-methylaminobenzyl alcohol	200 50	19.4 24.4	+21.3 +52.5
4-Amino-N-tert-butyl-3,5-dichloro- β -isopropoxyphenethylamine	200 50	14.8 20.9	- 7.5 +30.6
4-Amino-N-tert-butyl-3,5-dichloro- β -thoxyphenethylamine hydrochloride	200 50	15.9 22.8	+30.3 +86.9
Methyl-p-[3-[(4-amino-3,5-dichloro-4-hydroxyphenethyl)amino]propyl]benzoate	200 50	24.3 19.0	+22.6 - 4.1

TABLE II (continued)
Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
Methyl-4-[2-(tert-butylamino)-1-hydroxy- thyl]-2,6-dichlorocarbamate	50	27.9	+40.8
4'-[2-(Tert-butylamino)-1-hydroxyethyl]- -2',6'-dichloroacetanilide hydrochloride	200 50	21.8 23.4	+37.1 +47.2
5-[2-(Tert-butylamino)-1-hydroxyethyl]- -3-chloroantranilone nitrile	200 50	27.3 26.2	+90.9 +83.2
4-Amino-8-(benzyloxy)-N-tert-butyl-3,5- dichlorophenethylaniline hydrochloride	200 50	22.6 22.4	+58.0 +56.6
α-[(Tert-butylamino)methyl]-3,5-dichloro- 4-isopropylaminobenzyl alcohol	200 50 12 3	24.6 24.3 28.0 27.3	+72.0 +69.9 +95.8 +90.8

TABLE II (continued)
Evaluation of Test Compounds as Animal Growth Promoters

<u>Compound</u>	<u>Dosage</u> <u>(ppm)</u>	<u>Gain</u> <u>(grams)</u>	<u>% Gain Over</u> <u>Controls</u>
5-[2-(tert-butylamino)-1-hydroxyethyl]- anthranilnitrile	200 50	29.6 29.9	+79.4 +81.2
Methyl-5-[2-(tert-butylamino)-1-hydroxy- ethyl]-3-chloroanthranilate hydrochloride	200 50	24.4 20.1	+47.9 +21.8
4'-[2-Tert-butylamino)-1-hydroxyethyl] -2',6'-dichloroanilide	200 50	26.1 26.4	+58.2 +60.0
Benzyl-4-[2-(tert-butylamino)-1-hydroxy- ethyl]-2,6-dichlorocarbaniolate	50	25.1	+52.1
4-Amino-N-tert-butylamino-3,5-dichloro -8-(m thylthio)phenethylamine hydrochloride	200 50	25.4 25.3	+55.8 +55.2
N-Tert-butyl-3,5-dichloro-8-methoxy- phenethylamine hydrochloride	200 50	21.5 25.8	+50.3 +80.4

TABLE II (continued)
Evaluation of Test Compounds as Animal Growth Promoters

<u>Compound</u>	<u>Dosage</u> (ppm)	<u>Gain</u> (grams)	<u>% Gain Over</u> <u>Controls</u>
3-Bromo-5-[2-(tert-butylamino)-1-hydroxyethyl]- anthranilonitrile	200 50	16.1 24.2	+50.5 +126.2
4-Amino- α -[(tert-butylamino)methyl]-3-methyl- benzyl alcohol	100	20.8	+94.5
4-(Butylamino)- α -[(tert-butylamino)methyl]-3,5- dichlorobenzyl alcohol	200 50	19.3 19.4	+80.4 +81.3
2-Amino-3-bromo-5-[2-(tert-butylamino)-1- hydroxyethyl]benzamide	200 50	17.4 19.8	+62.6 +85.0
4-Amino- α -[(tert-butylamino)methyl]-3,5-dichloro- benzyl alcohol acetate (ester)	200 50	14.6 19.1	+36.4 +78.5

TABLE II (continued)
Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
3-Bromo-5-[2-tert-butylamino)-1-hydroxyethyl]- anthranilic acid	200 50	18.2 13.6	+70.1 +27.1
N-tert-butyl-3,5-dichloro-8-methoxy-4-methyl- aminophenethylamine hydrochloride	200 50	18.0 23.1	+68.2 +115.9
α -[(tert-butylamino)methyl]-3,5-dichloro-4- (hexylamino)benzyl alcohol	200 50	19.6 20.7	+83.2 +93.5
4-Amino- α -[(tert-butylamino)methyl]-3,5-dichloro- benzyl alcohol acetate (ester), acetate	200 50	14.4 18.7	+34.6 +74.8
4-Benzylamino- α -[(tert-butylamino)methyl]-3,5- dichlorobenzyl alcohol	200 50	15.7 16.4	+46.7 +53.3

TABLE II (continued)
Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
β -(allyloxy)-4-amino-N-tert-butyl-3,5-dichloro-phenethylamine	200 50	21.5 19.6	+100.9 +83.2
4'-[2-(tert-butylamino)-1-hydroxyethyl]-2',6'-dichlorobenzanilide	200 50	18.3 13.9	+71.0 +29.9
4-(allylamino)- α -[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol	200 50	20.2 21.9	+88.8 +104.7
4'-[3-(tert-butylamino)-1-hydroxyethyl]-2',6'-dichloroacetanilide acetate (ester), hydrochloride	200 50	25.8 16.2	+141.1 +51.4
N-(4-amino-3,5-dichloro- β -hydroxyphenethyl)-N-tert-butylacetamide acetate (ester)	200 50	18.7 15.0	+74.8 +40.2

TABLE II (continued)
Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
α -[(tert-Butylamino)methyl]-3,5-dichloro-4-cyclohexylaminobenzyl alcohol	100	23.0	+115.0
α -[(tert-Butylamino)methyl]-4-amino-3-chloro-5-methylbenzyl alcohol, hydrochloride	200 50	16.5 19.7	+54.2 +84.1

5

EXAMPLE 2Antilipogenic Evaluation of Test Compounds - Mouse Study

CFI female mice, 55 days old, are weighed in groups of 10 and allotted to cages to minimize weight variation among cages. Treatments are randomly assigned to cages.

Each of the treatments are tested in 3 replicates, i.e., in 3 cages of 10 mice each. There are 10 cages of 10 control mice each. Drugs are mixed in the diet at the dosage level indicated. Feed and water are offered ad libitum for 12-day test period. Feed spilled is collected during the test period. At the end of the test period, the collected feed is weighed and the mean feed consumption per cage of ten mice is determined for each treatment. The mice are weighed as a group of 10 and the weight gain determined. The mice are sacrificed by cervical dislocation. The right uterine fat pad of each mouse is removed. The fat pads for each cage of 10 mice are weighed as a unit.

Data obtained are reported in Table III. Data are reported as percent reduction in fat pad weight. Reduction in fat pad weights of animals is generally indicative of reduction of total body fat of the treated animals.

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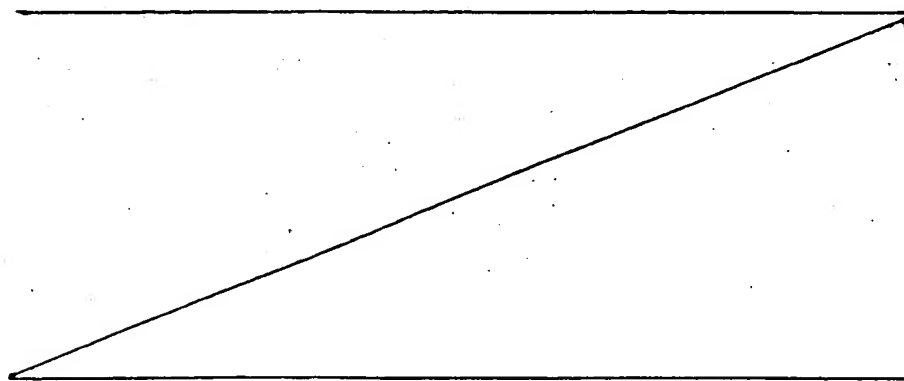


TABLE III
ANTILIPIDEMIC EVALUATION OF TEST COMPOUNDS - MOUSE STUDY

COMPOUND	DOSAGE (PPM)	% REDUCTION IN FAT	
		PAD WEIGHT VS CONTROLS	
α -[(Tert-butylamino)methyl]-3,5-dichloro-4-dimethylamino benzyl alcohol	200	-46.1	
	50	-44.8	
4-Amino-3,5-dichloro- α -[(3-phenyl-propyl)amino]methyl benzyl alcohol	200	-41.1	
	50	-36.2	
4-Amino-3,5-dichloro- α -[(α , α -dimethylphenethyl)amino] methyl benzyl alcohol hydrochloride	200	-43.1	
	50	-43.9	
α -[(Tert-butylamino)methyl]-3,5-dichloro-4-methylamino- benzyl alcohol	200	-51.0	
	50	-41.9	
4-Amino-N-tert-butyl-3,5-dichloro- β -isopropoxyphenethylamine	200	-57.0	
	50	-47.0	
4-Amino-N-tert-butyl-3,5-dichloro- β -ethoxyphenethylamine hydrochloride	200	-33.7	
	50	-15.3	

TABLE III (Continued)
ANTHRACENIC EVALUATION OF TEST COMPOUNDS - MOUSE STUDY

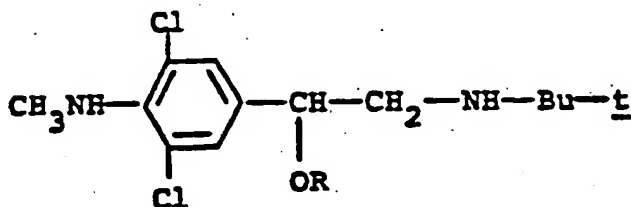
COMPOUND	DOSAGE (PPM)	% REDUCTION IN FAT	
		PAD WEIGHT VS CONTROLS	
Methyl-4-(3-[(4-amino-3,5-dichloro- β -hydroxyphenethyl) amino]propyl)benzoate	200 50	-27.7 -14.6	
Methyl-4-[2-(<u>tert</u> -butylamino)-1-hydroxyethyl]-2,6- dichlorocarbonilate	50	-23.5	
4 ¹ -[2-(<u>Tert</u> -butylamino)-1-hydroxyethyl]-2,6-dichloro- acetanilide hydrochloride	200 50	-27.1 - 8.8	
5-[2- <u>Tert</u> -butylamino-1-hydroxyethyl]-3-chloroanthranilonitrile	200 50	-45.9 -10.4	
4-Amino- β -(benzyloxy)-N- <u>tert</u> -butyl-3,5-dichloro- phenethylamine hydrochloride	200 50	-24.2 -18.4	
α -[(<u>Tert</u> -butylamino)methyl]-3,5-dichloro-4-isopropylaminobenzyl alcohol	200 50 12 3	-52.5 -22.6 - 6.3 -25.5	

TABLE III (Continued)
ANTILIPOGENIC EVALUATION OF TEST COMPOUNDS - MOUSE STUDY

COMPOUND	DOSAGE (PPM)	% REDUCTION IN FAT	
		PAD WEIGHT VS CONTROLS	
4 ¹ -[2-(<u>Tert</u> -butylamino)-1-hydroxyethyl]-2 ¹ ,6 ¹ - dichloro valeranilide	200	-33.2	
	50	-16.1	
Benzyl-4-[2-(<u>tert</u> -butylamino)-1-hydroxyethyl]- 2,6-dichlorocarbaniolate	50	-19.6	
Methyl-5-[2-(<u>tert</u> -butylamino)-1-hydroxyethyl]- 3-chloroanthranilate hydrochloride	200	- 5.9	
	50	- 5.8	
5-[2-(<u>Tert</u> -butylamino)-1-hydroxyethyl]anthranillo- nitrile	200	-41.5	
	50	-10.3	
4-[Amino-N- <u>tert</u> -butyl-3,5-dichloro- β -(methylthio) phenethylamine hydrochloride	200	-28.9	
	50	-16.2	
N- <u>tert</u> -butyl-3,5-dichloro- β -methoxyphenethylamine hydrochloride	200	-22.5	
	50	-10.4	

Example 35 N-tert-butyl-3,5-dichloro- α -methoxy-4-methylamino-
10 phenethylamine hydrochloride

A 7 g sample of α -[(tert-butylamino)methyl]-3,5-dichloro-4-methylaminobenzyl alcohol is added to 70 ml of thionyl chloride under N_2 atmosphere and the mixture is stirred for two hours. Excess thionyl chloride is removed in vacuo, and the glassy residue is dissolved in 50 ml of methanol. The solution is stirred for 1.5 hours and evaporated to dryness. The residue is dissolved in 100 ml of H_2O and extracted with 2 x 50 ml of CH_2Cl_2 . The aqueous layer is neutralized with solid $NaHCO_3$ and extracted with CH_2Cl_2 . The extract is dried ($MgSO_4$) and evaporated to dryness in vacuo to give 4.1 g of semi-solid, which after trituration with ethyl ether affords 1.07 g of the title compound, mp 220 - 221°C. Similarly, the following ethers are prepared:



30

35

-37-

5	<u>Alcohol</u>	<u>R</u>
	ethanol	C ₂ H ₅
	1-propanol	1-C ₃ H ₇
	2-propanol	2-C ₃ H ₇
	1-butanol	1-C ₄ H ₉
10	2-butanol	2-C ₄ H ₉
	1-hexanol	n-C ₆ H ₁₃
	benzyl alcohol	benzyl
	allyl alcohol	allyl
	4-methoxybenzyl alcohol	4-methoxybenzyl
15	4-chlorobenzyl alcohol	4-chlorobenzyl
	4-nitrobenzyl alcohol	4-nitrobenzyl
	4-methylbenzyl alcohol	4-methylbenzyl
	3,4-dimethylbenzyl alcohol	3,4-dimethylbenzyl
20	3,4-dimethoxybenzyl alcohol	3,4-dimethoxybenzyl
	3,4-dichlorobenzyl alcohol	3,4-dichlorobenzyl
	2-chlorobenzyl alcohol	2-chlorobenzyl
	2-methylbenzyl alcohol	2-methylbenzyl

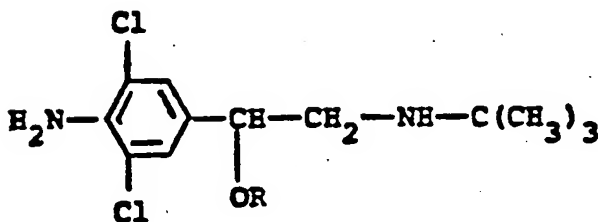
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Example 4

In the manner described in Example 3, the following ethers are prepared by substituting the corresponding alcohols for methanol.

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35



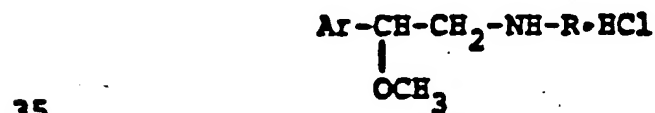
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5	<u>R</u>	<u>mp</u> °C
	benzyl	190-193
10	allyl	57- 59
	4-methoxybenzyl	
	4-chlorobenzyl	
	4-nitrobenzyl	
	4-methylbenzyl	
15	3,4-dimethylbenzyl	
	3,4-dimethoxybenzyl	
	3,4-dichlorobenzyl	
	phenyl	oil
20	4-chlorophenyl	
	4-methoxyphenyl	
	4-methylphenyl	
	2-chlorophenyl	
	4-nitrophenyl	

Example 5

25 N-tert-Butyl-3-chloro-5-cyano-B-methoxy-4-aminophenethyl-
amine hydrochloride

30 In the manner described in Example 3,
 α -[(tert-butylamino)methyl]-4-amino-3-chloro-5-cyano-
benzyl alcohol is converted into the title compound,
and, similarly, the following are also prepared:



	<u>Ar</u>	<u>R</u>
5	4-amino-3,5-dicyanophenyl	<u>t</u> -butyl
	4-amino-3-chloro-5-trifluoro- methylphenyl	<u>t</u> -butyl
	4-amino-3-chloro-5-trifluoro- methylphenyl	<u>i</u> -propyl
10	4-acetamido-3,5-dichlorophenyl	<u>t</u> -butyl
	4-acetamidophenyl	<u>t</u> -butyl
	4-amino-3-chloro-5-H ₂ N-CO- phenyl	<u>t</u> -butyl
	4-amino-3-chloro-5-HO-CO- phenyl	<u>t</u> -butyl
15	4-amino-3-chloro-5-methyl- phenyl	<u>t</u> -butyl
	4-amino-3-chloro-5-methoxy- phenyl	<u>t</u> -butyl
	4-amino-3-chloro-5-nitro- phenyl	<u>t</u> -butyl
20	4-amino-3-chloro-5-CH ₃ O-CO- phenyl	<u>t</u> -butyl
	4-amino-3-chloro-5-dimethyl- aminomethylphenyl	<u>t</u> -butyl
	4-amino-3-cyano-phenyl	<u>t</u> -butyl

25

Example 6

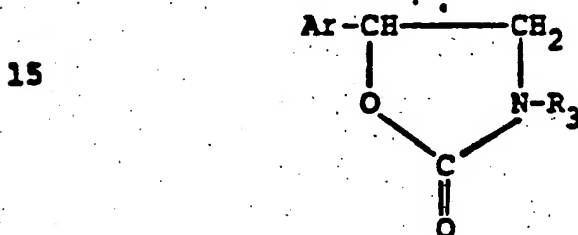
5-(4-amino-3,5-dichlorophenyl)-3-tert-butyl-2-oxazolidinone

In 10 ml of CH₂CL₂, 0.5 g of 4-amino-α-
 [(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol
 30 is stirred with 1 ml of Et₃N at -5°C and 2 ml of
 12.5% COCl₂ in benzene/5 ml of CH₂CL₂ is added over
 15 minutes. The resulting suspension is stirred
 20 minutes at 1°C and allowed to warm to room temperature
 with stirring for 1.5 hours. The mixture is evaporated
 35 to dryness, and the residue is chromatographed on
 silica gel with 1:1 hexane/CH₂CL₂ to afford 0.1 g of

5 oil which crystallizes to give the title compound,
mp 97 - 103°C.

In the same manner, α -[(allylamino)methyl]
-4-amino-3,5-dichlorobenzyl alcohol is allowed to
react with phosgene to afford 5-(4-amino-3,5-dichloro-
10 phenyl)-3-allyl-2-oxazolidinone.

Likewise, the following compounds are prepared
by this manner:



20	<u>Ar</u>	<u>R₃</u>
	3,5-dichlorophenyl	<u>t</u> -butyl
	3,5-dichlorophenyl	<u>i</u> -propyl
	4-acetamidophenyl	<u>t</u> -butyl
25	4-amino-3-chloro-5-cyanophenyl	<u>t</u> -butyl
	4-amino-3-chloro-5-trifluoro- methylphenyl	<u>t</u> -butyl
	3-chloro-4-acetamidophenyl	<u>t</u> -butyl
	3,5-dichloro-4-methylamino- phenyl	<u>t</u> -butyl
30	3,5-dichloro-4-ethylamino- phenyl	<u>t</u> -butyl
	3,5-dichloro-4- <u>i</u> -propyl- aminophenyl	<u>t</u> -butyl
	3,5-dichloro-4-acetamido- phenyl	<u>t</u> -butyl
35	3,5-dichloro-4-methoxy- carbonylamino-phenyl	<u>t</u> -butyl
	3,5-dichloro-4-benzyloxy- carbonylamino-phenyl	<u>t</u> -butyl

5	<u>Ar</u>	<u>R₃</u>
	3,5-dichloro-4-methyl-carbamoylaminophenyl	<u>t</u> -butyl
	4-amino-3-chloro-5-methylphenyl	<u>t</u> -butyl
10	4-amino-3-cyanophenyl	<u>t</u> -butyl
	4-amino-3-trifluoromethylphenyl	<u>t</u> -butyl
	4-amino-3-chloro-5-NH ₂ CO-phenyl	<u>t</u> -butyl
	4-amino-3-chloro-5-HOOC-phenyl	<u>t</u> -butyl
15	4-amino-3-chloro-5-CH ₃ OOC-phenyl	<u>t</u> -butyl
	4-amino-3-chloro-5-(CH ₃) ₂ NCH ₂ -phenyl	<u>t</u> -butyl
20	4-amino-3,5-dicyanophenyl	<u>t</u> -butyl

Example 7

4-Amino- α -[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol acetate

25 A mixture containing 1 g of 4-amino- α -[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol in 35 ml of CH₂Cl₂ at 10 - 15°C is stirred, and 0.37 g of Ac₂O and 0.5 ml of Et₃N are added dropwise. The reaction mixture is then allowed to warm to room
30 temperature, and the reaction is followed by thin-layer chromatography to completion. The mixture is evaporated to dryness in vacuo, and the yellow viscous liquid (1.5 g) is stirred with 50 ml of ethyl

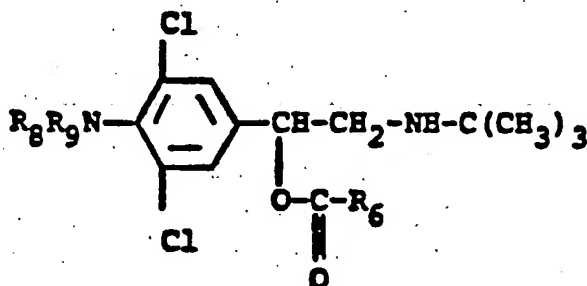
35

5 eth r to afford a yellow solid (0.84 g), mp 128 - 131°C.
 This material is shown by nuclear magnetic resonance
 spectroscopy and by neutralization with alkali to be
 the acetic acid salt. On treating 100 mg of this
 salt in 30 ml of CH₂Cl₂ with 30 ml of 10% aqueous
 10 NaOH, the salt is neutralized. The CH₂Cl₂ solution
 is dried (MgSO₄) and evaporated to dryness in vacuo
 to afford the viscous title compound. Analysis:
 Calcd for C₁₄H₂₀O₂N₂Cl₂: C, 52.67; H, 6.32; N, 8.78;
 Found: C, 52.38; H, 6.51; N, 8.88.

15 In the same manner, propionic anhydride,
 butyric anhydride, pivalic anhydride, and benzoic
 anhydride are allowed to react with 4-amino- α -[(tert-
 butylamino)methyl]-3,5-dichlorobenzyl alcohol (A) and
 α -[(tert-butylamino)methyl]-3,5-dichloro-4-methylamino-
 20 benzyl alcohol (B) respectively, to afford the propionate,
 butyrate, pivalate and benzoates of A and B.

Example 8

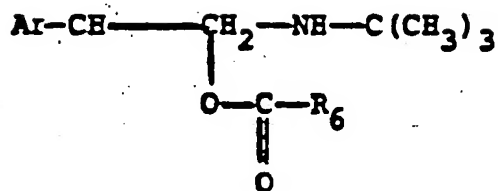
The following esters are prepared by the
 25 method of Example 7 by using the appropriate acid
 anhydride.



- 43 -

	<u>R₈</u>	<u>R₉</u>	<u>R₆</u>
5	H	CH ₃	CH ₃
	H	C ₂ H ₅	CH ₃
10	H	n-C ₃ H ₇	CH ₃
	H	2-C ₃ H ₇	CH ₃
	H	benzyl	CH ₃
	H	allyl	CH ₃
15	CH ₃	CH ₃	CH ₃
	H	CH ₃	C ₂ H ₅
	H	CH ₃ O-CO-	CH ₃
	H	CH ₃ NH-CO	CH ₃
20	H	CH ₃	n-C ₄ H ₉
	C ₂ H ₅	C ₂ H ₅	CH ₃
	n-C ₄ H ₉	n-C ₄ H ₉	CH ₃

25



30

35

	<u>Ar</u>	<u>R₆</u>
5	3,5-dichlorophenyl	2-C ₃ H ₇
	4-amino-3-chloro-5-cyanophenyl	CH ₃
	4-amino-3-chloro-5-trifluoro-	
10	methylphenyl	CH ₃
	4-amino-3-chloro-5-H ₂ NCO-phenyl	CH ₃
	4-amino-3-chloro-5-HOOC-phenyl	CH ₃
	4-amino-3-chloro-5-methylphenyl	CH ₃
15	4-amino-3-bromo-5-cyanophenyl	CH ₃
	4-amino-3-chloro-5-CH ₃ OCO-	
	phenyl	CH ₃
	4-amino-3-chloro-5-(CH ₃) ₂	
	NCH ₂ -phenyl	CH ₃
20	4-amino-3,5-dicyanophenyl	CH ₃
	4-amino-3-cyanophenyl	<u>t</u> -C ₄ H ₉

Example 9

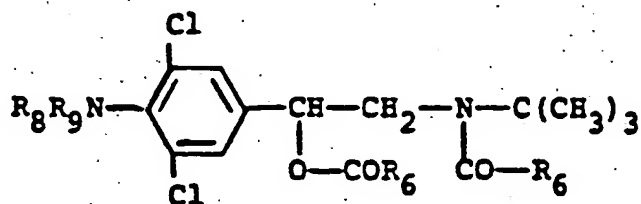
25 N-(4-amino-3,5-dichloro-β-hydroxyphenethyl)-N-tert
-butylacetamide acetate

30 A mixture containing 2.5 g of 4-amino-α-[(tert-butyl-
 amino)methyl]-3,5-dichlorobenzyl alcohol, 25 ml of
 pyridine and 10 ml of acetic anhydride is stirred
 for three hours and evaporated to dryness in vacuo
 with heating up to 70°C. The residue is treated
 with ice, 100 ml of CH₂Cl₂ and 50 ml of 10% NaOH solution.

- 5 The CH_2Cl_2 phase is separated, and the aqueous portion is further extracted with CH_2Cl_2 (2 x 50 ml). The combined CH_2Cl_2 solutions are dried (Na_2SO_4) and evaporated to dryness to afford a solid after scratching. The solid is washed with hexane and collected to
- 10 afford 2.61 g of the title compound, mp 126 - 136°C.

Similarly, by substituting the appropriate acid anhydrides, the following compounds are prepared.

15



20

R₈R₉R₆

H

CH₃CH₃

H

C₂H₅CH₃

H

2-C₃H₇CH₃

25

H

n-C₄H₉CH₃CH₃CH₃CH₃

H

CH₃O-COCH₃

H

CH₃NH-COCH₃

30

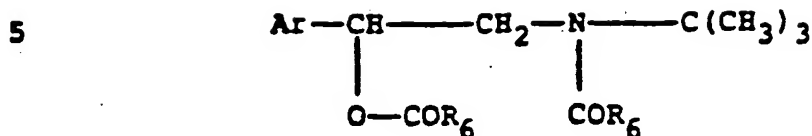
H

CH₃COCH₃

H

CH₃C₂H₅C₂H₅C₂H₅n-C₄H₉

35



	<u>Ar</u>	<u>R₆</u>
10	4-amino-3,5-dicyanophenyl	C ₂ H ₅
	4-amino-3-chloro- <i>t</i> -dimethyl- amino methylphenyl	CH ₃
	4-amino-3-chloro-5-CH ₃ OOC-phenyl	C ₂ H ₅
15	4-amino-3-chloro-5-methylphenyl	CH ₃
	3,5-dichlorophenyl	CH ₃
	4-amino-3-chloro-5-cyanophenyl	CH ₃
	4-amino-3-chloro-5-trifluoro- methylphenyl	CH ₃
20	4-amino-3-chloro-5-H ₂ NCO-phenyl	CH ₃

Example 10

25 4-Acetamido- α -[(*tert*-butylamino)methyl]-3,5-dichloro-
benzyl alcohol acetate

In 15 ml of CH₂Cl₂, 1.57 g of 4-acetamido-
- β -[(*tert*-butylamino)methyl]-3,5-dichlorobenzyl alcohol
is suspended and stirred while 1.2 g of triethylamine
30 in 30 ml of 30 ml of CH₂Cl₂ is added, followed by
0.7 g of acetic anhydride in 15 ml of CH₂Cl₂. The
mixture is stirred for 20 hours and then is washed
with 100 ml of 10% NaOH solution. The organic phase
is separated, dried (Na₂SO₄) and evaporated to dryness
35 in vacuo. The residue is dissolved in 30 ml of ethanol
and a trace of H₂O is added, followed by 10% HCl
to acidify. The mixture is evaporated to dryness
in vacuo and the residue is crystallized from acetone/
hexane (30 ml/5 ml). This aff rds 1.35 g, mp. 254 -
257°C d c., f the titl compound.

-47-

Similarly, by replacing acetic anhydride with propionic anhydride, butyric anhydride, pivalic anhydride, and benzoic anhydride, the corresponding propionate, butyrate, pivalate, and benzoate esters are prepared.

Example 11

10 α -[(tert-Butylamino)methyl]-m-hydroxybenzyl alcohol acetate

In the manner described in Example 10 m-(benzyloxy)- α -[(tert-butylamino)methyl]benzyl alcohol is converted to m-(benzyloxy)- α -[(tert-butylamino)-methyl]benzyl alcohol acetate. This material is then debenzylated to give α -[(tert-butylamino)methyl]-m-hydroxybenzyl alcohol acetate.

Example 12

20 5-(p-Aminophenyl)-3-tert-butyl-2-oxazolidinone

In 270 ml of CH_2Cl_2 , 12.97 g of α -[(tert-butylamino)methyl]-p-nitrobenzyl alcohol is dissolved. The solution is cooled to -5°C and 54 ml of 12.5% phosgene in benzene is added slowly. After the addition is completed, the mixture is stirred for 3.5 hours and poured on ice. The organic phase is separated, and the aqueous layer is extracted with CH_2Cl_2 (2 X 100 ml). The combined organic layers are washed with saturated NaHCO_3 solution (2 X 250 ml), 100 ml of H_2O and dried over MgSO_4 . The solution is evaporated to dryness to give 16.3 g, which is recrystallized from MeOH twice to afford 12.58 g of 3-tert-butyl-5-(p-nitrophenyl)-2-oxazolidinone, mp $123 - 125^\circ\text{C}$. This product (10 g) is dissolved in 200 ml of MeOH and hydrogenated

35

-48-

5 over 6 g of Raney nicke at 51 p.s.i.g at 40°C to give,
after filtration and evaporation, 8.21 g of 5-(p-
aminophenyl)-3-tert-butyl-2-oxazolidinone,
mp 125 - 129°C.

Example 13

10 α -[(tert-butylamino)-methyl]3,5-dichloro-4-dimethyl-
aminobenzyl alcohol

A mixture containing 50 g of p-fluoroaceto-
phenone and 150 ml of 40% aqueous dimethylamine is
warmed in a pressure bottle at 90 - 100°C. After
15 two hours, a pale yellow oil is formed. The mixture
is cooled, and the oil solidifies. The solid is
collected and washed well with H₂O to give 54.93
of p-dimethylaminoacetophenone, mp 101 - 103°C, after
heptane recrystallization. A 72 g sample of this
20 acetophenone is heated with 129 g of N-chlorosuccinimide
in 700 ml of toluene to reflux temperature and maintained
at this temperature for 35 minutes. The mixture
is cooled and filtered. The filter cake is washed
with 200 ml of toluene, and the filtrate and wash
25 solution are evaporated to dryness in vacuo to afford
66 g of oil. This oil is chromatographed on SiO₂ =
with 40% hexane/CH₂Cl₂ to give 38.9 g of 3,5-dichloro-
4-dimethylaminoacetophenone as a yellow oil. A 5.22 g
sample of this oil is added portionwise to 2.75 g
30 of SeO₂ in 20 ml of dioxane and 0.7 ml of H₂O at
55 - 60°C. This mixture is heated at reflux temperature
for 4.5 hours, cooled and filtered through siliceous
earth. The filter cake is washed with 20 ml of dioxane.
The dioxane solutions are cooled to 15°C and 2.77 g
35 of t-butylamine is added dropwis to afford a tan
precipitate. After stirring 15 minutes at room temperature,

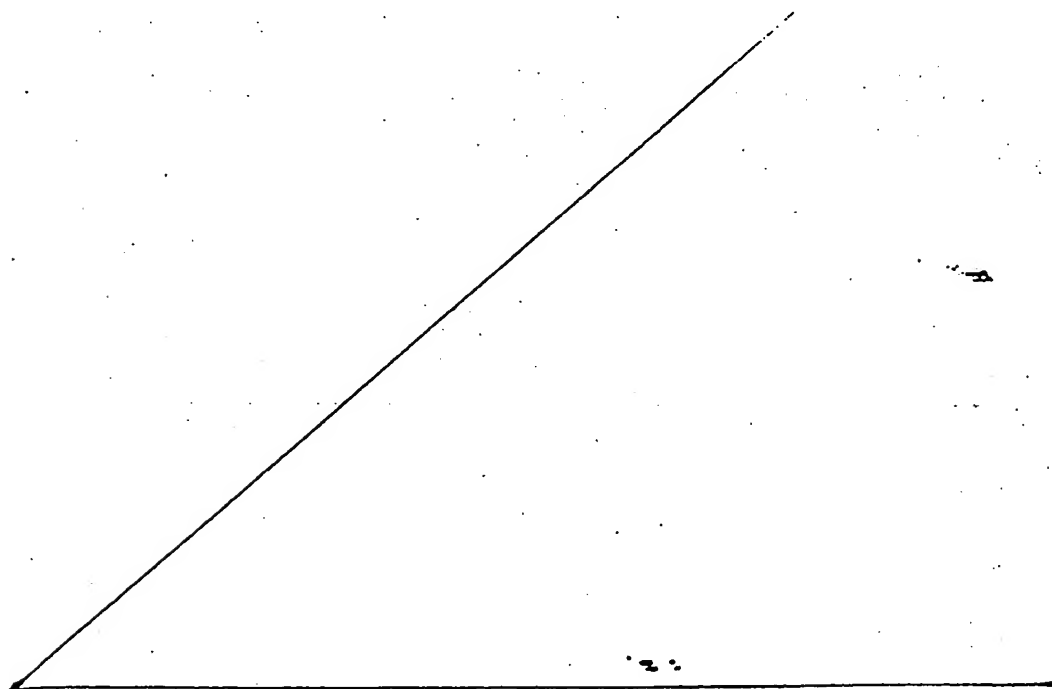
5 the mixture is diluted with 200 ml of ethanol, cooled
to 5°C and 7 g of NaBH_4 is added portionwise. After
15 hours, the mixture is treated with 300 - 400 g
of ice and 200 ml of H_2O at below 10°C. The mixture
is stirred to dissolve all solids and extracted with
10 300 ml of CH_2Cl_2 . The CH_2Cl_2 layer is washed with
100 ml of H_2O , dried (MgSO_4) and evaporated to dryness
in vacuo to give 5.6 g of orange oil. This oil is
dissolved in ethyl ether, decolorized with activated
carbon and concentrated to 15 ml. On cooling, crystals
15 are obtained. The title product is collected as
white crystals, mp 96 - 99°C.

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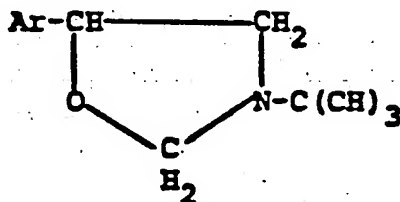


5

EXAMPLE 145-(4-amino-3,5-dibromophenyl)-3-~~tert~~-butyloxazolidine

A mixture containing 2 g of 4-amino-3,5-dibromo- α -[(tert-butylamino)methyl]benzyl alcohol and 5 ml of 37% formalin solution in 20 ml of toluene containing a few crystals of p-toluene sulfonic acid is heated at reflux to azeotrope water. After three hours, the mixture is cooled, diluted to 75 ml with CH_2Cl_2 and washed with 10% aqueous NaOH solution (2x20 ml). The aqueous portion is further extracted with 10 ml of CH_2Cl_2 and the combined organic extracts are dried (MgSO_4) and evaporated to dryness in vacuo to afford 1.6 g of clear brown oil. A chemical ionization mass spectrographic analysis gives a Mass + H^+ of 377, which is correct for the title compound. The nuclear magnetic resonance proton spectrum reveals a singlet at $\delta 4.53$ in CDCl_3 indicative of the $\text{O}-\text{CH}_2-\text{N}$ group in the title compound.

In the same manner, the following oxazolidines are prepared by substituting the corresponding aryethanolamines for 4-amino-3,5-dibromo- α -[(tert-butylamino)methyl]benzyl alcohol.



30

35

5

EXAMPLE 17

α -[~~tert~~-butylamino)methyl]-3,5-dichloro-4-methylamino-
benzyl alcohol

p-Methylaminoacetophenone is prepared and chlorinated by method described in Example 29 to give
10 3,5-dichloro-4-methylaminoacetophenone. This ketone (18 g) in 200 ml of CHCl_3 is stirred and 4.65 ml of Br_2 in 50 ml of CHCl_3 is added dropwise. After the addition is completed, the mixture is stirred an additional 20 minutes and warmed to reflux temperature for 25 minutes.
15 The mixture is cooled, 100 ml of H_2O is added and saturated Na_2CO_3 solution is added carefully until the mixture is neutral. The CHCl_3 layer is separated and the aqueous layer is further extracted with 100 ml of CH_2Cl_2 . The combined extracts are dried (MgSO_4) and
20 evaporated to dryness to afford 16.3 g of the phenacyl bromide. This material (16 g) in 80 ml of EtOH is stirred at 12-15°C and 40 ml of t-butylamine is added dropwise. After the addition is completed the mixture is stirred for 10 minutes at 12-15°C and then cooled to
25 5° and 4 g of NaBH_4 is carefully added. After stirring for 0.5 hours, the mixture is allowed to warm to room temperature and stirring is continued for 0.75 hours. The mixture is poured on 300 ml of ice with stirring and the resulting mixture is extracted with 300 ml of
30 CH_2Cl_2 . The CH_2Cl_2 extract is dried (MgSO_4) and evaporated to dryness in vacuo to give a yellow oil. Trituration of this residue with ethyl ether affords 7.45 g of the title compound, which melts at 98-101°C after recrystallization from ethyl ether.

35

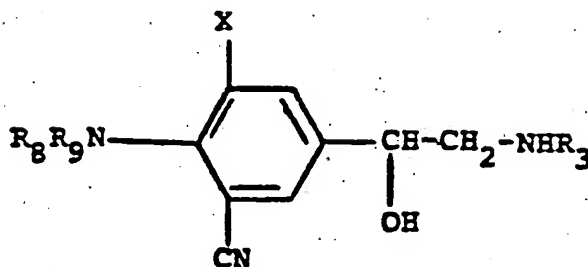
5

EXAMPLE 185-[2-(tert-butylamino)-1-hydroxyethyl]anthranilonitrile

- A mixture containing 48.86 g of p-amino-acetophenone in 490 ml of toluene is stirred while 64.5 g of N-bromosuccinimide is added in portions over 10 0.5 hours at below 40° C. After 15 minutes, the mixture is washed with H₂O (4x100 ml). The solution is dried (MgSO₄) and evaporated to dryness to afford 70.53 g of 4-amino-3-bromoacetophenone, mp 59-62°C. A 35 g sample of this material in 180 ml of dry dimethylformamide is 15 stirred and heated at reflux with 17.57 g of Cu₂(CN)₂ for 6 hours under N₂ atmosphere. Subsequently, 180 ml of FeCl₃/HCl solution (40 g FeCl₃·6H₂O/10 ml concentrated HCl/60 ml H₂) is added and the mixture is heated for 20 minutes at 60-70°C and poured into 350 ml of H₂O. 20 The aqueous mixture is extracted with CH₂Cl₂ and the extracts are washed with H₂O, saturated NaHCO₃ solution and H₂O, respectively. The CH₂Cl₂ solution is evaporated to dryness in vacuo and the residue is recrystallized from 95% EtOH to afford 14.25 g, mp 155-159°C, of 25 4-amino-3-cyanoacetophenone. A 4.8 g sample of this product in 100 ml of EtOAc and 100 ml of CHCl₃ containing 13.32 g of CuBr₂ is heated at reflux temperature for 20 minutes. The mixture is further heated after 20 ml of EtOH is added and then filtered while still hot. The 30 filter cake is washed with 50 ml of hot 20% MeOH/CH₂Cl₂ and the combined organic solutions are evaporated to dryness in vacuo. The residue is stirred in 25 ml of CH₂Cl₂ and the solid is collected and washed with CH₂Cl₂ to give 8.08 g of the phenacyl bromide. This 35 material is added to 50 ml of t-BuNH₂ in 100 ml of

5 EtOH at 5° under N₂ atmosphere. After 10 minutes of
stirring, the mixture is allowed to warm to 30°C to give
a solution. This solution is cooled to 10° and 4 g of
NaBH₄ is added in portions. After 45 minutes, the
mixture is allowed to warm (42°C) and kept at 20°C until
10 the exotherm subsides. The mixture is then evaporated
to dryness and the residue is washed with H₂O. The
residue is dried and treated with 200 ml of boiling
MeOH and the hot MeOH solution is filtered. The filter
cake is further washed with hot MeOH and the combined
15 filtrates are concentrated to afford crystals. This
solid is recrystallized from MeOH/2-PrOH to afford
2.08 g, mp 184-186°C, of the title compound.

In a similar manner, the following related
compounds are prepared starting with the appropriate
20 acetophenone:



	<u>R₈</u>	<u>R₉</u>	<u>R₃</u>	<u>X</u>
5	H	H	2-C ₃ H ₇	H
	H	CH ₃	<u>t</u> -butyl	H
	CH ₃	CH ₃	<u>t</u> -butyl	H
10	H	C ₂ H ₅	<u>t</u> -butyl	H
	H	n-C ₃ H ₇	<u>t</u> -butyl	H
	H	2-C ₃ H ₇	<u>t</u> -butyl	H
	H	n-C ₄ H ₉	<u>t</u> -butyl	H
	H	CH ₃	2-C ₃ H ₇	H
15	H	benzyl	<u>t</u> -butyl	H
	C ₂ H ₅	C ₂ H ₅	<u>t</u> -butyl	Cl
	<u>n</u> -C ₃ H ₇	<u>n</u> -C ₃ H ₇	<u>t</u> -butyl	Cl
	<u>n</u> -C ₄ H ₉	<u>n</u> -C ₄ H ₉	<u>t</u> -butyl	Cl

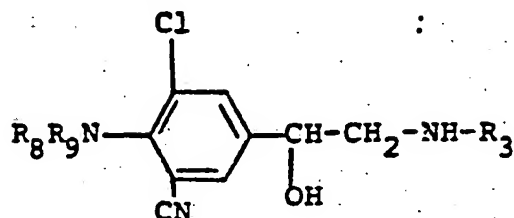
EXAMPLE 19

20 3-chloro-5-[2-(tert-butylamino)-1-hydroxyethyl]-
anthranilonitrile

In 100 ml of toluene, 5 g of 4-amino-3-cyanoacetophenone is heated at reflux temperature for 20 minutes with 4.2 g of N-chlorosuccinimide. The mixture is cooled and filtered. The filtrate is further heated at reflux temperature for 2 hours. The precipitate is collected and washed with H₂O. The remaining solid is treated with 0.75 ml of Br₂/14 ml of CHCl₃ added to 75 ml of CHCl₃ and 4.9 ml of EtOH. The mixture is evaporated to dryness and the residue is slurried with CH₂Cl₂, collected and washed with CH₂Cl₂ to afford 2.84 g of the phenacyl bromide. This material is allowed to react with t-BuNH₂ and reduced with NaBH₄ by the procedure of Example 18 to afford the title compound, mp 128-138°C.

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In a similar manner, the following compounds are prepared:



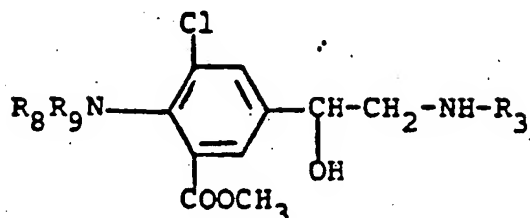
<u>R₈</u>	<u>R₉</u>	<u>R₃</u>
H	H	2-propyl
H	CH ₃	<u>t</u> -butyl
CH ₃	CH ₃	<u>t</u> -butyl
H	C ₂ H ₅	<u>t</u> -butyl
H	2-propyl	<u>t</u> -butyl
H	n-butyl	<u>t</u> -butyl
H	benzyl	<u>t</u> -butyl

EXAMPLE 20

5-[2-(tert-butylamino)-1-hydroxyethyl]-3-chloro-anthranilic acid, methyl ester, hydrochloride

A mixture containing 1.36 g of 5-[2-(tert-butylamino)-1-hydroxyethyl]-3-chloroanthranilonitrile in 21 ml of 50% aqueous NaOH and 21 ml of EtOH is stirred under N₂ for 0.5 hours. The mixture is evaporated to remove EtOH and acidified to pH 3 and further evaporated to dryness in vacuo. The residue treated several times with MeOH and evaporated to dryness. The solid is then treated with a solution which is prepared from 40 ml of MeOH and 2 ml of acetyl chloride. After allowing to stand overnight, the mixture is filtered and the filtrate is evaporated to dryness. The filter cake is also washed with MeOH and added to preceding filtrate. The residue is dissolved in acetone, filtered, and evaporated to dryness. The solid is triturated with Et₂O and filtered to give 1.49 g, mp 95-115°C, of the title compound.

In a similar manner, the following related esters are prepared:



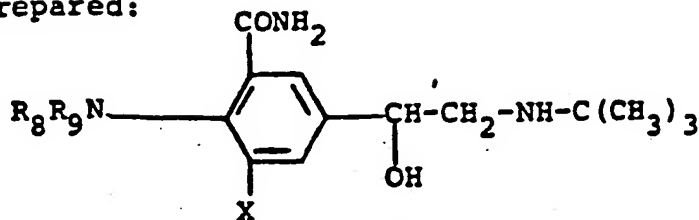
<u>R₈</u>	<u>R₉</u>	<u>R₃</u>
H	H	2-propyl
H	CH ₃	<u>t</u> -butyl
CH ₃	CH ₃	<u>t</u> -butyl
H	C ₂ H ₅	<u>t</u> -butyl
H	<u>n</u> -propyl	<u>t</u> -butyl
H	<u>n</u> -butyl	<u>t</u> -butyl
H	benzyl	<u>t</u> -butyl
H	allyl	<u>t</u> -butyl
C ₂ H ₅	C ₂ H ₅	<u>t</u> -butyl
<u>n</u> -C ₄ H ₉	<u>n</u> -C ₄ H ₉	<u>t</u> -butyl
<u>n</u> -C ₃ H ₇	<u>n</u> -C ₃ H ₇	<u>t</u> -butyl

EXAMPLE 21

2-Amino-3-bromo-5-[2-(tert-butylamino)-1-hydroxyethyl]-benzamide

A mixture containing 1.02 g of 3-bromo-5-[2-(tert-butylamino)-1-hydroxyethyl]anthranilonitrile in 25 ml of H₂O, 5 ml of 50% NaOH and 30 ml of EtOH is stirred and heated at 55-65°C under N₂ atmosphere for 1.25 hours. The mixture is evaporated to remove EtOH and extracted with CHCl₃. The CHCl₃ extract is washed with 25 ml of 2% NaOH, dried (MgSO₄) and evaporated to dryness to afford 0.74 g. This solid is stirred with pentane and filtered to afford 0.6 g, mp 135-145°C, of the title compound.

Similarly, the following compounds are prepared:



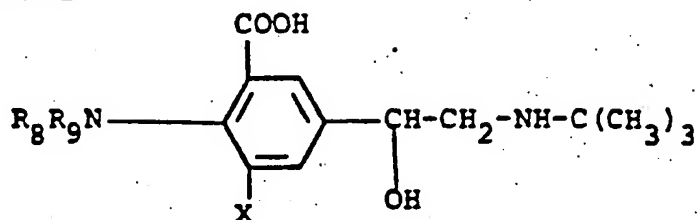
<u>R₈</u>	<u>R₉</u>	<u>X</u>
H	CH ₃	Cl
H	H	Cl
H	C ₂ H ₅	Cl
CH ₃	CH ₃	Cl
H	2-C ₃ H ₇	Cl
H	n-C ₄ H ₉	Cl
H	CH ₃	Br
H	benzyl	Cl
C ₂ H ₅	C ₂ H ₅	Cl
n-C ₃ H ₇	n-C ₃ H ₇	Cl
n-C ₄ H ₉	n-C ₄ H ₉	Cl

EXAMPLE 22

3-bromo-5-[2-(tert-butylamino)-1-hydroxyethyl]-anthranilic acid

A mixture containing 2 g of 3-bromo-5-[2-(tert-butylamino)-1-hydroxyethyl]anthranilonitrile in 10 ml of 50% NaOH, 50 ml of H₂O and 60 ml of EtOH is stirred and heated to reflux temperature under N₂ for an hour. The EtOH is evaporated and the aqueous mixture mixed with 50 ml of H₂O and 50 ml of CHCl₃. The CHCl₃ layer is removed and the interfacial brown oil is collected, added to 10 ml of MeOH, 5 ml of H₂O and this mixture is acidified to pH 5. After stirring for an hour, the off-white solid is collected, washed with H₂O and dried to give 0.8 g, mp 221.5 C dec., of the title compound.

Similarly, the following compounds are prepared:



<u>R₈</u>	<u>R₉</u>	<u>X</u>
H	H	Cl
H	CH ₃	Cl
CH ₃	CH ₃	Cl
H	CH ₃	Br
H	2-C ₃ H ₇	Cl
H	n-C ₄ H ₉	Cl
H	benzyl	Cl
C ₂ H ₅	C ₂ H ₇	Cl
n-C ₃ H ₇	n-C ₃ H ₇	Cl
n-C ₄ H ₉	n-C ₄ H ₉	Cl

EXAMPLE 23

5-(3-hydroxyphenyl)-3-tert-butyl-2-oxazolidinone

In the manner described in Example 8, m-benzyloxy)- α -[tert-butylamino)methyl]benzyl alcohol is converted to the oxazolidinone compound by treatment with phosgene. Subsequently debenzylation is completed to give the title compound.

EXAMPLE 24

5-(3-hydroxyphenyl)-3-tert-butyloxazolidine

In the manner described in Example 12, m-(benzyloxy)- α -[(tert-butylamino)methyl]benzyl alcohol is reacted with formaldehyde to afford the oxazolidin derivative, which is debenzylated by the procedure of Example 10 to give the title compound.

EXAMPLE 25

5 4-amino-N-tert-butyl-3,5-dichloro- β -(methylthio)-
 phenethylamine hydrochloride

 In the manner described in Example 3,
N-tert-butyl-3,5-dichloro- β -chloro-4-aminophenethyl-
amine hydrochloride is prepared. An 11 g sample of
10 this product is portionwise added to 5 ml of methyl
 mercaptan in 100 ml of dry ethylenedichloride at
 -10°C to 0°C. The mixture is stirred and allowed
 to rise gradually to room temperature over a four
 day period. The mixture is filtered, the filter cake
15 is washed with ethylenedichloride (2x500 ml). The
 solid is dispersed in 200 ml of H₂O, cooled to 5°C
 and basified with 6N NaOH solution to give a white
 oil, which is extracted with CH₂Cl₂ (3x100 ml). The
 CH₂Cl₂ extract is dried (MgSO₄) and evaporated to
20 dryness to give 6.41 g of dark green oil. This oil
 is stirred in HCl/isopropanol and the mixture is
 evaporated to dryness. The residue is stirred in
 35 ml of ethyl ether for 16 hours and filtered to
 give 3.63 g, mp 178-181°C dec. This solid is heated
25 in refluxing ethyl acetate and filtered to give
 2.07 g, mp 188-193°C. Recrystallization from 75 ml
 of ethylenedichloride affords 1.45 g of the title
 compound, mp 191-196°C.

 The title compound is also obtained by
30 adding 5-10 fold excess of sodium mercaptide in
 tetrahydrofuran at 0-10°C and by following the above
 workup.

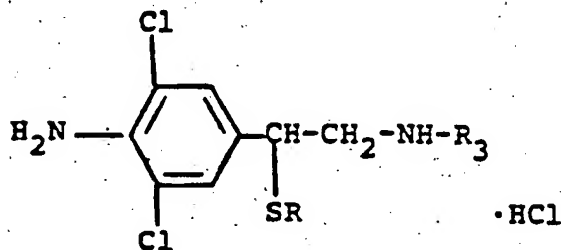
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EXAMPLE 26

In the same manner as described in Example 25, the following thioethers are prepared by substituting methyl mercaptan with the corresponding mercaptans:

10



15

20

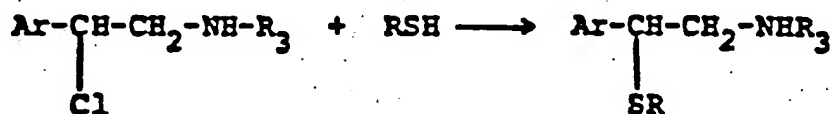
25

<u>R</u>	<u>R₃</u>
methyl	2-propyl
ethyl	<u>t</u> -butyl
2-propyl	<u>t</u> -butyl
<u>n</u> -butyl	<u>t</u> -butyl
<u>t</u> -butyl	<u>t</u> -butyl
<u>n</u> -hexyl	<u>t</u> -butyl
phenyl	<u>t</u> -butyl
benzyl	2-propyl

EXAMPLE 27

In the manner described in Example 25, substitution of the corresponding chloro compound for N-tert-butyl-3,5-dichloro-β-chloro-4-aminophenethylamine hydrochloride and adding the appropriate mercaptans afford the following thioethers:

30



35

	Ar	R	R ₃
5	4-amino-3-cyanophenyl	methyl	2-propyl
	4-methylamino-3,5-dichlorophenyl	methyl	<u>t</u> -butyl
	4-amino-3-chloro-5-trifluoromethyl	methyl	<u>t</u> -butyl
	4-amino-3-chloro-5-cyanophenyl	methyl	<u>t</u> -butyl
10	4-amino-3-chloro-5-cyanophenyl	ethyl	<u>t</u> -butyl
	4-acetamido-3,5-dichlorophenyl	methyl	<u>t</u> -butyl
	4-amino-3-chloro-5-H ₂ NCO-phenyl	methyl	<u>t</u> -butyl
	4-amino-3-chloro-5-HOCO-phenyl	methyl	<u>t</u> -butyl
	4-amino-3-chloro-5-methylphenyl	ethyl	<u>t</u> -butyl
15	4-amino-3-chloro-5-methoxyphenyl	<u>n</u> -butyl	<u>t</u> -butyl
	4-amino-3-chloro-5-nitrophenyl	methyl	<u>t</u> -butyl
	4-amino-3-chloro-5-CH ₃ O-CO-phenyl	methyl	<u>t</u> -butyl

EXAMPLE 283,5-dichloro-4-(N,N-diethylamino)acetophenone

20 A sample (2.5 g) of 4-amino-3,5-dichloro-acetophenone in 10 ml of acetic anhydride and 25 ml of pyridine is stirred and heated at reflux temperature for 20 hours. The mixture is evaporated to dryness, and the residue is treated with ice and

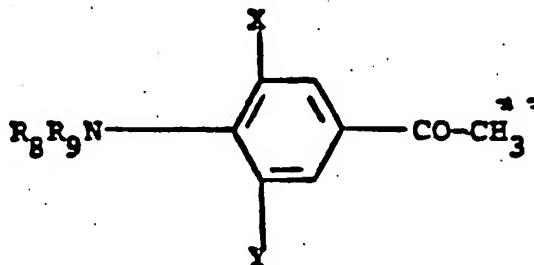
25 10% NaOH solution and extracted with CH₂Cl₂ (3x50-ml). The extracts are dried (Na₂SO₄) and evaporated to dryness to give 2.42 g of semisolid, which is purified by chromatography over SiO₂ using CH₂Cl₂ as eluent to afford 1.06 g of 4-(N,N-diacetylamino)-

30 3,5-dichloroacetophenone as an oil. This material is dissolved in 10 ml of tetrahydrofuran (THF) under N₂ atmosphere and 18 ml of 1M BH₃·THF is added dropwise. The mixture is stirred until the reaction is complete and H₂O is added cautiously. The mixture

5 is evaporated to remove THF and 20 ml of H_2O and
10 ml of 10% NaOH are added. This aqueous mixture
is extracted with CH_2Cl_2 (3x25 ml) and the extracts
are dried (Na_2SO_4) and evaporated to dryness to yield
0.68 g of the desired alcohol. This product (0.3 g) in
10 2 ml of CH_2Cl_2 is added to 0.32 g of pyridinium
chlorochromate (PCC) in 2 ml of CH_2Cl_2 . After
1.25 hours, an additional 0.3 g of PCC is added and
after another 0.5 hours, the solution is decanted
and the residue is washed with 10 ml of CH_2Cl_2 . The
15 combined CH_2Cl_2 solutions are diluted with 50 ml of
 CH_2Cl_2 and washed with 10 ml of saturated Na_2CO_3
solution and 10 ml of H_2O and dried (Na_2SO_4). The
solution is evaporated to dryness to afford a
residue which is chromatographed on SiO_2 with
20 CH_2Cl_2 as eluent to yield 0.04 g of the title compound
as an oil (NMR in $CDCl_3$: δ 1.0 (6H, triplet),
2.5 (3H, singlet), 3.25 (4H, quartet), 7.83 (2H, singlet).
The monoethylaminoacetophenone is also obtained as
a solid (0.12 g) as the second component.

25 This 3,5-dichloro-ethylaminoacetophenone
is further reacted with propionic anhydride, reduced
and reoxidized in the above manner to afford 3,5-
dichloro-N-ethyl-N-propylaminoacetophenone.

30 In a similar manner the following 4-(N,N-
dialkylamino)-acetophenones which are required for
preparing 4-(N,N-disubstituted amino) compounds of
formula I are prepared:



	<u>R₈</u>	<u>R₉</u>	<u>X</u>	<u>Y</u>
5	<u>n-C₃H₇</u>	<u>n-C₃H₇</u>	Cl	Cl
	<u>n-C₄H₉</u>	<u>n-C₄H₉</u>	Cl	Cl
	<u>C₂H₅</u>	<u>n-C₃H₇</u>	Cl	Cl
	<u>C₂H₅</u>	<u>C₂H₅</u>	Cl	CH ₃
10	<u>C₂H₅</u>	<u>C₂H₅</u>	Cl	CF ₃
	<u>C₂H₅</u>	<u>C₂H₅</u>	Cl	NO ₂
	<u>C₂H₅</u>	<u>C₂H₅</u>	Cl	Br
	<u>C₂H₅</u>	<u>C₂H₅</u>	Cl	OCH ₃

EXAMPLE 29

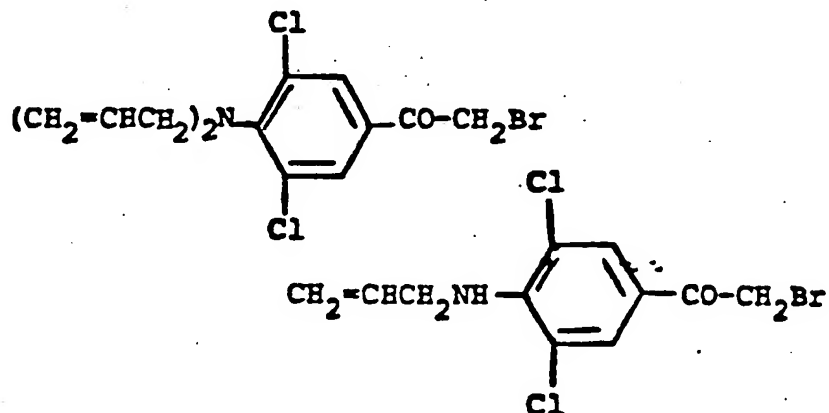
α -[(tert-butylamino)methyl]-3,5-dichloro-4-diethyl-aminobenzyl alcohol

In the manner described in Example 13, 3,5-dichloro-4-diethylaminoacetophenone is oxidized with SeO₂ and reductively alkylated with t-BuNH₂/NaBH₄ to afford the title compound, mp 93-96°C.

Similarly, α -[(tert-butylamino)methyl]-3,5-dichloro-4-(n-dipropyl)aminobenzyl alcohol and α -[(tert-butylamino)methyl]-3,5-dichloro-4-(n-dibutyl)-aminobenzyl alcohol are prepared

EXAMPLE 30

2-bromo-3',5'-dichloro-4'-diallylaminoacetophenone and 4'-(allylamino)-2-bromo-3',5'-dichloroacetophenone



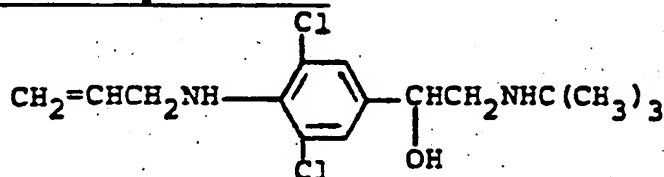
5 Triethylamine (17.0 g, 0.168 mol) is
added in one portion to allyl bromide (105.9 g,
0.875 mol) under a nitrogen atmosphere. The resulting
white emulsion gives an exotherm to 70°C and becomes
a thick white solid mass within 5 minutes. The
10 solution formed with the addition of ~100 ml of
DMF is stirred for 1 hour at 70-95°C. A solution
of 4'-amino-2-bromo-3',5'-dichloroacetophenone
(25.0 g, 0.088 mol) in 50 ml of DMF is added in
one portion and the resulting brown reaction mixture
15 is maintained at 80-90°C for 2 hours. The progress
of the reaction is frequently checked by thin layer
chromatography (SiO₂/CH₂Cl₂/hexanes (1/1)) since
prolonged heating results in the decomposition of
both starting material and products. The reaction
20 mixture is poured into 1.5l of H₂O and is stirred for
0.5 hours. After a second aqueous trituration, the
residual brown semi-solids are stirred with ~150 ml
of CCl₄ for 0.5 hours to form a suspension. The
yellowish-brown solids are collected by filtration
25 and are air dried to give 14.9 g (59.6%) of recovered
phenacyl bromide starting material. The CCl₄ filtrate
is stirred with MgSO₄, filtered and concentrated to
yield 9.42 g of a brown syrup. Gradient elution
(hexanes/CH₂Cl₂ (10/0 → 8/2) flash chromatography
30 on a 9"x2" column of Silica Gel 60 gives two major
fractions:

(A) 1.82 g (5.7%) of a faster moving amber
syrup, identified as 2-bromo-3',5'-dichloro-4'-
diallylaminoacetophenone by IR(neat) 1680 cm⁻¹,
35 NMR (CDCl₃) δ 7.93 (s, 2, AR-H), 6.25-5.55 (complex
m, 2, CH=), 5.40-4.95 (complex m, 4, CH₂=),
4.40 (s, 2, CH₂Br) and 3.87 (m resembling d, 4,
J=6Hz, CH₂N); chemical ionization mass spectrum
(M + H)⁺ = 3.62; and

5 (B) 3.49 g (12.2%) of a slower moving brown syrup, identified as 4'-(allylamino)-2-bromo-3',5'-dichloroacetophenone by IR(neat) 3330, 1670 cm^{-1} ; NMR(CDCl_3) δ 7.83 (s, 2, AR-H), 6.35-5.65 (complex m, 1, CH=), 5.50-5.00 (complex m, 2, CH_2 =), 4.84 (br t, 1, NH), 4.37 (s, 2, CH_2Br) and 4.20 (br m, 2, CH_2N); chemical ionization mass spectrum ($\text{M} + \text{H}^+$) = 322.

EXAMPLE 31

15 4-(Allylamino)- α -[(*tert*-butylamino)methyl]-3,5-dichlorobenzyl alcohol



20 A solution of 4'-(allylamino)-2-bromo-3',5'-dichloroacetophenone (2.88 g, 8.92 mmol) in 10 ml is added dropwise over 1 hour to a stirred solution of *t*-butylamine (1.34 g, 18.3 mmol) in 20 ml of THF. The reaction temperature is maintained at -24 $^{\circ}$ -13 $^{\circ}$ C by cooling in a dry ice- CCl_4 bath. The resulting amber suspension is warmed to room temperature over 30 minutes and is stirred at 21-22 $^{\circ}$ C for 1.5 hours. Sodium cyanoborohydride (2.80 g, 44.6 mmol) is added in two portions over 25 5 minutes to give a thick tan suspension with an exotherm from 22-25 $^{\circ}$ C. Glacial acetic acid (~10 ml) is added dropwise to gradually form a yellow solution which is stirred at room temperature for 3 days. The reaction mixture is poured into a solution of 35 100 ml of H_2O and 100 ml of saturated aqueous NaCl which is then adjusted to pH7 with 10% Na_2CO_3 and extracted thr times with Et_2O . The combined

5 extracts are shaken with two portions of diluted
aqueous HCl which are combined, neutralized with
10% Na₂CO₃ to pH8 and extracted three times with
Et₂O. After stirring the combined extracts with
anh. K₂CO₃, the pale yellow-green solution is
10 filtered and concentrated to yield 2.04 g (72.1%)
of a pale yellow syrup, identified as 4-(allylamino)-
α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl
alcohol by IR(neat) 3400 cm⁻¹; NMR(CDCl₃)
δ7.32 (s, 2, Ar-H), 6.35-5.60 (complex m, 1, CH=),
15 5.45-4.95 (complex m, 2, CH₂=), 4.52 (d of d, 1,
Ar-CH), 3.97 (overlapping m, 3, Ar-NHCH₂),
3.03 (br s, 2, NH and OH), 2.68 (m, 2, CH₂N) and
1.13 (s, 9, C(CH₃)₃); chemical ionization mass
spectrum (M + M)⁺ = 317. The CH₂Cl₂/CH₃OH/conc. NH₄OH
20 (80/19/1) shows one major spot (R_F = 0.6) with nine
trace impurities. The syrup gradually crystallizes
to a tan solid on standing.

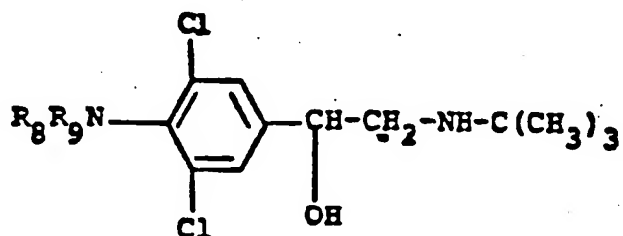
EXAMPLE 32

25 N-tert-butyl-m-hydroxy-β-methylthiophenethylamine
hydrochloride

By using the procedure of Example 3 and
substituting methyl mercaptan for methanol as in
Example 25 the title compound is prepared.

EXAMPLE 33

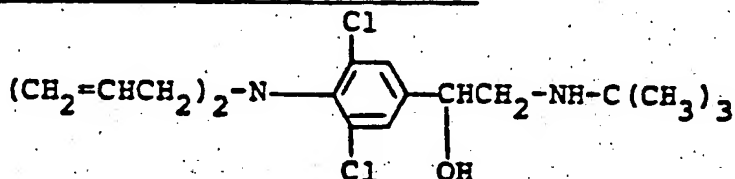
30 The following compounds are prepared by the
method of Example 13:



5	<u>R₈</u>	<u>R₉</u>	<u>mp °C-</u>
	H	1-C ₄ H ₉	oil
	H	1-C ₆ H ₁₃	62-64
	H	C ₂ H ₅	209 (HCl salt)
	H	benzyl	85-89
10	H	cyclopentyl	oil
	H	cyclohexyl	194-198 (HCl salt)
	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -		

EXAMPLE 34

15 α -[(tert-butylamino)methyl]-3,5-dichloro-4-
diallylaminobenzyl alcohol



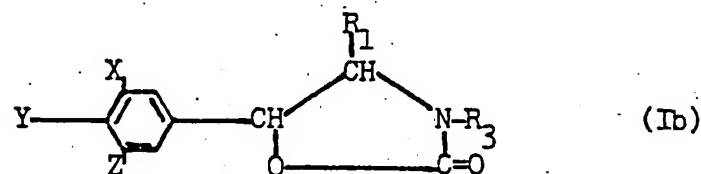
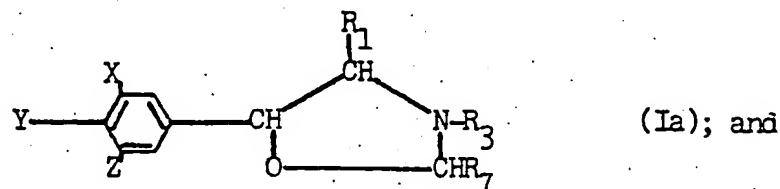
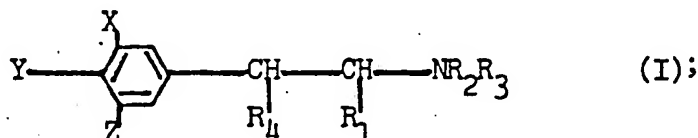
20 The title compound is prepared using the procedure described for the preparation of 4-(allylamino)- α -[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol (Example 31). The pale yellow

25 syrup, which gradually crystallizes on standing, is identified by IR(neat) 3300 and 1630 cm⁻¹; NMR(CDCl₃) δ 7.26 (s, 2, Ar-H), 6.23-5.54 (complex m, 2, CH=), 5.32-4.87 (complex m, 4, CH₂=), 4.48 (m, 1, Ar-CH), 3.78 (m resembling d, 4, J-6Hz, Ar-NCH₂), 3.4-2.0 (br s, 2, NH and OH), 2.62 (m, 2, CH₂N) and 1.13 (s, 9, C(CH₃)₃); chemical ionization mass spectrum (M + H)⁺ = 357, corresponding to that

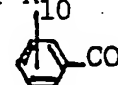
30 expected of the title compound.

CLAIM

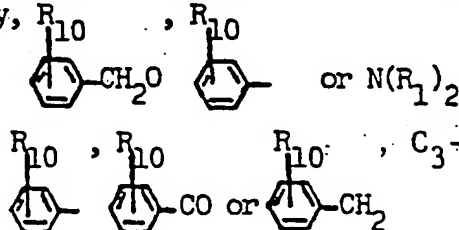
1. An animal feed composition comprising a balanced diet and from 0.01 to 400 grams per ton of feed of a compound having a formula selected from the group consisting of:



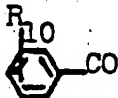
wherein, X is hydrogen, halogen or -CN; Y is hydrogen, NR_8R_9 or NHCOR_5 ; Z is hydrogen, halogen, OH, CN, CF_3 , COOR_1 , CONH_2 , $\text{C}_1\text{-C}_4$ alkyl or $\text{C}_1\text{-C}_4$ alkoxy; R_1 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl; R_2 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_5$ alkanoyl or R_{10} ; R_3 is hydrogen,



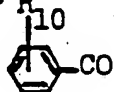
R_6 is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_5$ alkanoyl, R_{10} , R_{10} , R_{10} , $\text{C}_3\text{-C}_4$ alkenyl;



R_7 is hydrogen, C_1-C_4 alkyl or phenyl; R_8 is hydrogen, C_1-C_4 alkyl or C_3-C_4 alkenyl; R_9 is hydrogen, C_1-C_6 alkyl, C_4-C_6 cycloalkyl, C_3-C_4 alkenyl, or benzyl; and when R_8 and R_9 are taken together with the nitrogen to which they are attached, they represent pyrrolidino; R_{10} is chloro, dichloro, methyl, dimethyl, methoxy, dimethoxy or nitro; R_{11} is C_1-C_6 alkyl, phenyl or benzyl; with the provisos that when R_3 is phenyl, 2-hydroxyethyl, α,α -dimethylphenethyl, C_3-C_6 cycloalkyl, benzyl, methoxypropyl, 3-phenylpropyl, or 3-(4-carbomethoxyphenyl)propyl, R_2 is hydrogen; and when R_3 is hydroxyethyl, R_4 is hydroxyl and the compound is (I); and when R_6 is alkanoyl or R_{10} , R_2 and R_3 are substituents other than

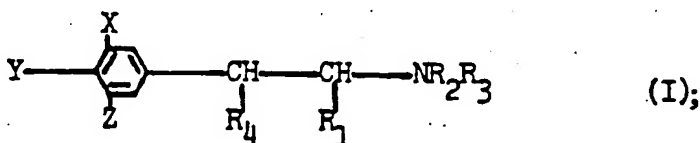


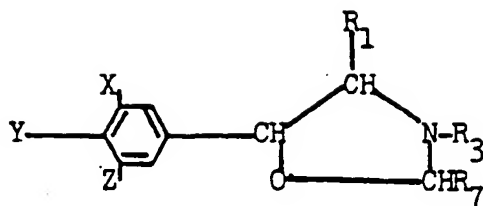
hydrogen, except when R_3 is an alkyl or a substituted alkyl group which contains a tertiary carbon attached to nitrogen; and when Y is hydrogen, X and Z are halogen, and R_2 is hydrogen, C_2-C_5 alkanoyl or R_{10} , R_3 is isopropyl, 2-butyl, and *t*-butyl; and when



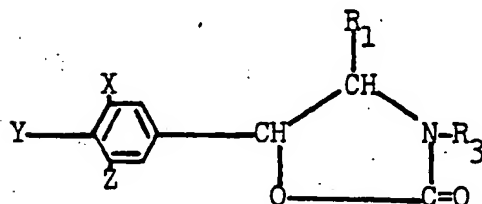
R_8 is C_1-C_4 alkyl or C_3-C_4 alkenyl, R_9 is C_1-C_4 alkyl or C_3-C_4 alkenyl; and when Z is OH, X and Y are hydrogen; and that at least one of X, Y and Z represents a substituent other than hydrogen; and when X is -CN, Z is -CN; and when Z is hydroxyethyl, R_4 is OH; and when Z is a group other than halogen, Y is NR_8R_9 or $NHCO R_5$; and when R_5 is $N(R_1)_2$, R_4 is OH; and further provided that when X is hydrogen or halogen, and Y is hydrogen, NH_2 or $NHCO R_5$, and Z is hydrogen, halogen or OH, then R_4 cannot be hydrogen, OH or OR_6 where R_6 is C_1-C_6 alkyl; racemic mixtures of the above - identified compounds and the optically active isomers, and non-toxic, pharmacologically acceptable acid addition salts thereof.

2. A method for the preparation of an animal feed composition comprising admixing an animal feed with from 0.01 to 400 grams per ton of feed of a compound having a structure selected from the group consisting of:





(Ia); and



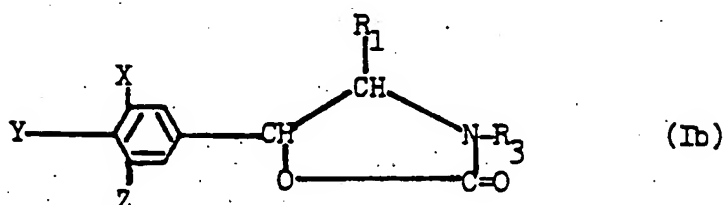
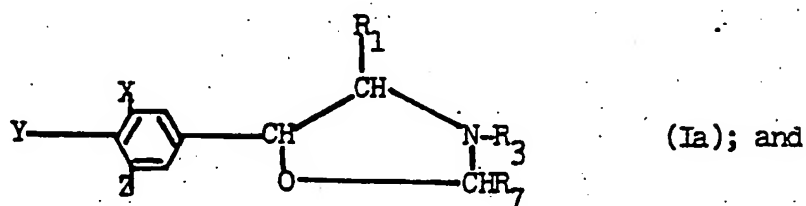
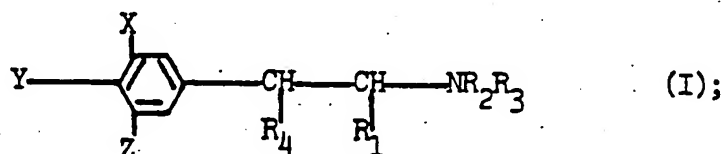
(Ib)

wherein X, Y, Z, R₁, R₂, R₃, R₄ and R₇, are as defined in claim 1 above.

3. A composition according to claim 1 wherein said compound is selected from the group consisting of: N-tert-butyl-3,5-dichloro-8-methoxy-4-methylaminophenethylamine; α-[(tert-butylamino)methyl]-3,5-dichloro-4-isopropylaminobenzyl alcohol; 5-[2-(tert-butylamino)-1-hydroxyethyl]-3-chloroanthranilonitrile; 5-[2-(tert-butylamino)-1-hydroxyethyl]anthranilonitrile; methyl-5-[2-(tert-butylamino)-1-hydroxyethyl]-3-chloroanthranilate; 4'-[2-(tert-butylamino)-1-hydroxyethyl]-2',6'-dichloroanilide; benzyl-4-[2-(tert-butylamino)-1-hydroxyethyl]-2,6-dichlorocarbamate; 5-acetylanthranilonitrile; 4-amino-N-tert-butyl-3,5-dichloro-8-(methylthio)phenethylamine; N-tert-butyl-3,5-dichloro-8-methoxyphenethylamine; α-[(tert-butylamino)-methyl]-3,5-dichloro-4-methylaminobenzyl alcohol; α-[(tert-butylamino)methyl]-3,5-dichloro-4-dimethylaminobenzyl alcohol; 4-amino-3,5-dichloro-α-[(3-phenylpropyl)amino]methylbenzyl alcohol; 4-amino-3,5-dichloro-α-[[α,α-dimethylphenethyl)amino]methylbenzyl alcohol; 4-amino-N-tert-butyl-3,5-dichloro-8-ethoxyphenethylamine; methyl-p-(3-[(4-amino-3,5-dichloro-8-hydroxyphenethyl)amino]propyl)benzoate; methyl-4-[2-(tert-butylamino)-1-hydroxyethyl]-2,6-dichlorocarbamate; 4'-[2-(tert-butylamino)-1-hydroxyethyl]-2',6'-dichloroacetanilide; 5-[2-(tert-butylamino)-1-hydroxyethyl]-3-chloroanthranilonitrile; 4-amino-8-(benzyloxy)-N-tert-butyl-3,5-dichlorophenethylamine and the non-toxic, pharmaceutically acceptable acid addition salts thereof.

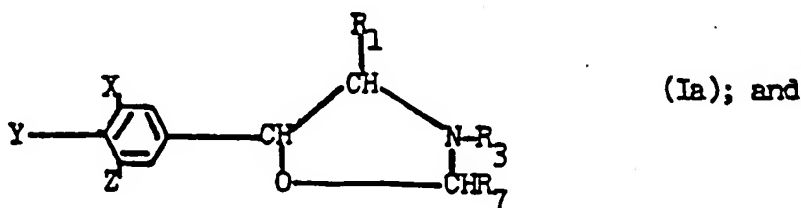
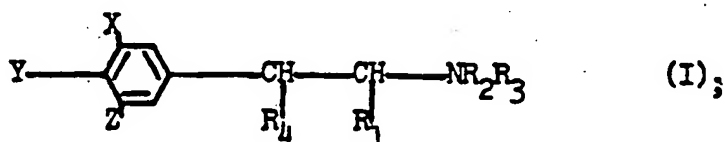
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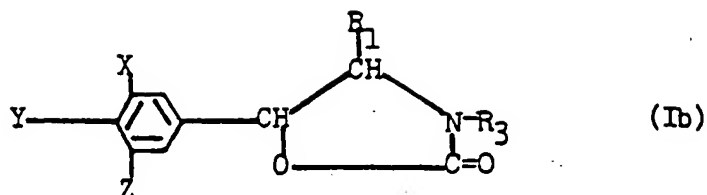
4. An animal feed supplement useful for enhancing the growth rate and lean meat deposition in warm-blooded animals comprising from about 75% to 95% by weight of a compound having formula selected from the group consisting of:



wherein X, Y, Z, R₁, R₂, R₃, R₄ and R₇, are as defined in claim 1 above and from about 5% to 25% by weight of a suitable carrier or diluent.

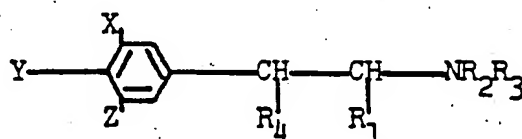
5. An injectable composition useful for enhancing the growth rate and lean meat deposition in warm-blooded animals comprising as an active ingredient a compound having a formula selected from the group consisting of:





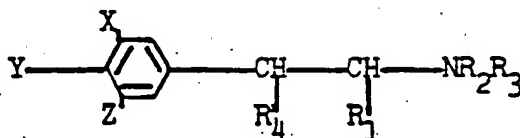
wherein X, Y, Z, R₁, R₂, R₃, R₄ and R₇, are as defined in claim 1 above, and a pharmaceutically acceptable carrier.

6. A composition according to claim 5 wherein the active ingredient is administered to warm-blooded animals in an amount sufficient to provide said animals with from 0.001 to 100 mg/kg/day of body weight of the active ingredient having the formula:



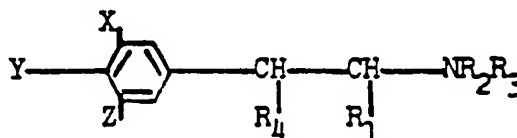
wherein X, Y, Z, R₁, R₂, R₃, and R₄, are as defined in claim 1 above.

7. An implant useful for increasing the dressed carcass weight of meat-producing animals and enhancing the lean meat to fat ratio thereof comprising as the active ingredient a compound having the structure:

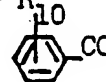


wherein X, Y, Z, R₁, R₂, R₃ and R₄ are as described in claim 1 above, and a pharmaceutically acceptable carrier.

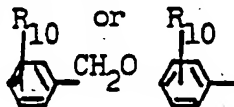
8. A compound of the formula:



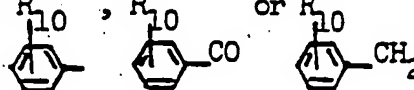
wherein X is hydrogen, halogen or -CN; Y is hydrogen, NR_8R_9 or NHCOR_5 ; Z is halogen, -CN, CF_3 , COOR, CONH_2 , $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ alkoxy, NO_2 or $\text{C}_1\text{-C}_4$ dialkylaminomethyl; R_1 is hydrogen or $\text{C}_1\text{-C}_4$ alkyl; R_2 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_5$ alkanoyl or R_{10} ;



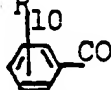
R_3 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_4$ alkenyl, phenyl or benzyl; R_4 is OH, OR_6 , or OR_{11} ; R_5 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ alkoxy, R_{10} or R_{10} ;



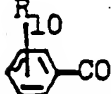
R_6 is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_5$ alkanoyl, R_{10} , R_{10} or R_{10} ; R_8 is



hydrogen, $\text{C}_1\text{-C}_4$ alkyl or $\text{C}_3\text{-C}_4$ alkenyl; R_9 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_4\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_4$ alkenyl or benzyl; R_{10} is hydrogen, chloro, dichloro, methyl, dimethyl, methoxy, dimethoxy or nitro; R_{11} is $\text{C}_1\text{-C}_6$ alkyl, phenyl, benzyl; with the provisos that when Y is NH_2 , NHCH_3 , NHC_2H_5 , R_4 is OR_6 or SR_{11} ; and when Y is hydrogen, X and Z are halogen, R_2 is hydrogen, $\text{C}_2\text{-C}_5$ alkanoyl or R_{10} and R_3 is isopropyl, 2-butyl



or t-butyl; and when X is -CN, Z is -CN; and when R_6 is alkanoyl or R_{10} , R_2 and R_3 are substituents other than hydrogen, except when



R_3 is an alkyl or a substituted alkyl group which contains a tertiary carbon attached to nitrogen; and when R_8 is $\text{C}_1\text{-C}_4$ alkyl or $\text{C}_3\text{-C}_4$ alkenyl, R_9 is $\text{C}_1\text{-C}_4$ alkyl or $\text{C}_3\text{-C}_4$ alkenyl; and further provided that when X and Z are halogen and Y is hydrogen or NH_2 then R_4 cannot be hydrogen, OH or OR_6 where R_6 is $\text{C}_1\text{-C}_6$ alkyl; racemic mixtures of the above - identified compounds and the optically active isomers, and non-toxic pharmacologically acceptable acid addition salts thereof.

9. A compound according to claim 8 wherein said compound is:

N-tert-butyl-3,5-dichloro- β -methoxy-4-methylaminophenethylamine; α -[(tert-butylamino)methyl]-3,5-dichloro-4-isopropylaminobenzyl alcohol; 5-acetylanthranilonitrile; 4-amino-N-tert-butyl-3,5-dichloro- β -(methylthio)phenethylamine; α -[(tert-butylamino)methyl]-3,5-dichloro-4-dimethylaminobenzyl alcohol; 4-amino- β -(benzyloxy)-N-tert-butyl-3,5-dichlorophenethylamine; 4-(allylamino)- α -[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol, and the non-toxic, pharmaceutically acceptable acid addition salts thereof.